Re-evaluation Decision RVD2017-01

Glyphosate

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Executive Summary

Health Canada's primary objective in regulating pesticides is to protect Canadians' health and their environment. Pesticides must be registered by Health Canada's Pest Management Regulatory Agency (PMRA) before they can be imported, sold, or used in Canada. Pesticides must go through rigorous science-based assessments before being approved for sale in Canada.

All registered pesticides must be re-evaluated by the PMRA on a cyclical basis to make sure they continue to meet modern health and environment safety standards and continue to have value. In 2015, the PMRA published the outcome of its extensive re-examination of glyphosate for public comment (PRVD2015-01), which concluded that the products containing glyphosate do not present unacceptable risks to human health or the environment when used according to the revised product label directions.

During this re-examination, the PMRA assessed the potential human health risk of glyphosate from drinking water, food, occupational and bystander exposure, as well as the environmental risk to non-target organisms. Both the active ingredient and formulated products were included in the re-evaluation. The assessment was carried out based on available information provided by the manufacturer of the pesticide, as well as a large volume of published scientific literature, monitoring information (for example, ground water and surface water) and reviews conducted by other regulatory authorities.

The overall finding from the re-examination of glyphosate is highlighted as follows:

- Glyphosate is not genotoxic and is unlikely to pose a human cancer risk.
- Dietary (food and drinking water) exposure associated with the use of glyphosate is not expected to pose a risk of concern to human health.
- Occupational and residential risks associated with the use of glyphosate are not of concern, provided that updated label instructions are followed.
- The environmental assessment concluded that spray buffer zones are necessary to mitigate potential risks to non-target species (for example, vegetation near treated areas, aquatic invertebrates and fish) from spray drift.
- When used according to revised label directions, glyphosate products are not expected to pose risks of concern to the environment.
- All registered glyphosate uses have value for weed control in agriculture and non-agricultural land management.

All comments received during the consultation process were taken into consideration. These comments and new data/information resulted in only minor revisions to the proposed regulatory decision described in PRVD2015-01. Therefore, the PMRA is granting continued registration of products containing glyphosate with requirements of additional label updates to further protect human health and the environment.

To comply with this decision, the required label changes must be implemented on all product labels sold by registrants no later than 24 months after the publication date of this document.

Re-evaluation Decision for Glyphosate

After a re-evaluation of the herbicide glyphosate, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting continued registration of products containing glyphosate for sale and use in Canada.

An evaluation of available scientific information found that products containing glyphosate do not present risks of concern to human health or the environment when used according to the revised label directions. As a requirement for the continued registration of glyphosate uses, new risk reduction measures are required for the end-use products registered in Canada. No additional data are being requested at this time.

Findings of the re-evaluation of glyphosate were first presented for public consultation in the Proposed Re-evaluation Decision PRVD2015-01, *Glyphosate*,[1] whereas this Re-evaluation Decision (RVD2017-01)[2] summarizes the Agency's final decision on the re-evaluation of glyphosate and the reasons for it.

Comments received during the consultation period were taken into consideration. These comments and new data/information resulted in revisions to some parts of the risk assessments, however, they did not result in substantial changes to the proposed regulatory decision as described in PRVD2015-01. Appendix I of this document summarizes the comments received and provides the PMRA's response.

To comply with this decision, the required mitigation measures must be implemented on all product labels sold by registrants no later than 24 months after the publication date of this document. Registrants of the products containing glyphosate will be informed of the specific requirements affecting their product registration(s) and of the regulatory options available to them.

What Does Health Canada Consider When Making a Re-evaluation Decision?

Health Canada's pesticide re-evaluation program considers potential risks[3] as well as the value[4] of pesticide products to ensure they meet modern standards established to protect human health and the environment. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information.

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

3 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

4 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact".

In 2010, Health Canada published a re-evaluation work plan for glyphosate (REV2010-02) outlining the focus of this re-evaluation and indicating that the PMRA is working cooperatively with the United States Environmental Protection Agency. As part of this re-evaluation, the effect of Polyethoxylated Tallow Amines (POEA) and the metabolite and transformation product Aminomethylphosphonic acid (AMPA) are also included.

What Is Glyphosate?

Glyphosate is a broad-spectrum, non-selective herbicide. It controls many annual weeds, perennial weeds, woody brush and weedy trees. It is registered for use on a wide variety of sites including terrestrial feed and food crops, terrestrial non-food, non-feed and fibre crops, and for non-agricultural, industrial and residential weed management for non-food sites, forests and woodlots, outdoor ornamentals and turf.

Glyphosate is present as the free acid or as a salt in formulated end use products. Glyphosate products are formulated as solutions, pastes or tablets and can be applied using ground or aerial application equipment. Other application techniques are also used to apply glyphosate, such as with a wiper or wick applicator, cut stump or stem injection treatment. The rate of application ranges from 0.25 to 4.32 kg a.e./ha, depending on weed species (for example, annual vs. perennial) and use site. All products containing glyphosate currently registered under the authority of the *Pest Control Products Act* are listed in Appendix II.

Health Considerations

Can Approved Uses of Glyphosate Affect Human Health?

Products containing glyphosate are unlikely to affect your health when used according to label directions.

Potential exposure to glyphosate may occur through diet (food and water), or when handling and applying the product, or by entering treated sites. When assessing health risks, two key factors are considered: the levels at which no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Glyphosate is of low acute oral, dermal and inhalation toxicity. It is severely irritating to the eyes, non-irritating to skin and does not cause an allergic skin reaction.

Registrant-supplied short and long term (lifetime) animal toxicity tests, as well as numerous peer-reviewed studies from the published scientific literature were assessed for the potential of glyphosate to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects.

The most sensitive endpoints for risk assessment were clinical signs of toxicity, developmental effects, and changes in body weight. The young were more sensitive than the adult animals. However, the risk assessment approach ensures that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Food and Water

Dietary risks from food and water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Potential acute and chronic dietary exposures to glyphosate were estimated from residues of glyphosate and relevant metabolites in both treated crops and drinking water. Exposure to different subpopulations, including children and women of reproductive age, were considered. The acute dietary exposure estimate from food and drinking water at the 95th percentile represents 31% of the acute reference dose (ARfD) for females 13-49 years of age, and ranges from 12% to 45% of the ARfD for all other population subgroups. The chronic dietary exposure estimate for the general population represents 30% of the acceptable daily intake (ADI). Exposure estimates for population subgroups range from 20% of the ADI (for adults aged 50 years or older) to 70% of the ADI (for children 1-2 years old). Thus, acute and chronic dietary risks are not of concern.

The *Food and Drugs Act* prohibits the sale of adulterated food; that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose a health risk concern.

Canadian MRLs for glyphosate are currently specified for a wide range of commodities (MRL database http://pr-rp.hc-sc.gc.ca/mrl-lrm/index-eng.php). Residues in all other agricultural commodities, including those approved for treatment in Canada but without a specific MRL, are regulated under Subsection B.15.002(1) of the Food and Drug Regulations, which requires that residues do not exceed 0.1 ppm. Separate MRLs have been established for the trimethylsulfonium (TMS) cation, the major metabolite of the glyphosate-TMS salt, in/on a variety of commodities. Given that all glyphosate-TMS-containing products have been discontinued in Canada, all MRLs for the TMS cation will be revoked.

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern when used according to label directions.

Residential exposure may occur from the application of products containing glyphosate to residential lawns, and turf (including golf courses), gardens and trees. Residential handler exposure could occur from mixing, loading and applying domestic-class glyphosate products. These products can be applied as a liquid by a manually pressurized handwand, backpack, sprinkler can and ready-to-use sprayer.

Residential postapplication exposure may occur for persons performing activities on treated areas. This includes areas treated by residential handlers as well as residential areas treated by commercial applicators. Exposure is predominantly dermal. Incidental oral exposure may also occur for children (1 to <2 years old) playing in treated areas.

For all domestic class products, the target dermal and inhalation margins of exposure (MOE) were met for adults applying glyphosate and are not of concern. Residential postapplication activities also met the target dermal MOE for all populations (including golfers) and are not of concern. For incidental oral exposure, the target oral MOEs were met for children (1 to <2 years old) and are not of concern.

Non-occupational scenarios were aggregated with background (chronic) dietary exposure (food and drinking water). The resulting aggregate risk estimates reached the target MOE for all uses and are not of concern.

Non-occupational risks from bystander dermal exposure are not of concern.

Bystander exposure may occur when the general public enter non-cropland areas (for example, hiking through forests or parks) that have recently been treated with glyphosate. The resulting risk estimates associated with bystander dermal exposure met the target MOE for all populations and are not of concern.

Occupational Risks from Handling Glyphosate

Occupational risks to handlers are not of concern when used according to label directions.

Risks to handlers are not of concern for all scenarios. Based on the precautions and directions for use on product labels reviewed for this re-evaluation, risk estimates associated with mixing, loading and applying activities met the target dermal and inhalation MOEs and are not of concern.

Postapplication risks are not of concern for all uses.

Postapplication occupational risk assessments consider exposures to workers entering treated sites in agriculture. Based on the current use pattern for agricultural scenarios reviewed for this re-evaluation, postapplication risks to workers performing activities, such as scouting, met the target dermal MOEs and are not of concern. A minimum restricted entry interval of 12 hours is required for agricultural sites.

Polyethoxylated Tallow Amines (POEA)

POEA is a family of several compounds that are used as surfactants in many glyphosate products registered in Canada. No human health risks of concern were identified for these end-use products, provided that they contain no more than 20% POEA by weight. All of the currently registered glyphosate end-use products in Canada meet this limit.

Environmental Considerations

What Happens When Glyphosate Is Introduced Into the Environment?

When used according to revised label directions, glyphosate products are not expected to pose risks of concern to the environment. Labelled risk-reduction measures mitigate potential risks posed by glyphosate formulations to non-target plants and freshwater/marine/estuarine organisms.

When glyphosate is released into the environment, it can enter soil and surface water. Glyphosate breaks down in soil and water and is not expected to remain for long periods of time. Glyphosate produces one major break down product in soil and water, aminomethyl phosphonic acid (AMPA), which can last in the environment. Carryover of glyphosate and AMPA into the next growing season is not expected to be significant. Glyphosate and AMPA are not expected to move downward through the soil and are unlikely to enter groundwater.

Glyphosate dissolves readily in water but is expected to move into sediments in aquatic environments. Glyphosate is not expected to enter the atmosphere. Glyphosate and AMPA are unlikely to accumulate in animal tissues.

Certain glyphosate formulations include a surfactant composed of POEA compounds. At high enough concentrations, POEA is toxic to aquatic organisms but is not expected to remain in the environment. While, in general, glyphosate formulations that contain POEA are more toxic to freshwater and marine/estuarine organisms than formulations that do not contain POEA, they do not pose risks of concern to the environment when used as directed on the label.

In the terrestrial environment the only risk identified was for terrestrial plants, therefore, spray buffer zones are required to reduce exposure to sensitive terrestrial plants.

Glyphosate formulations pose a negligible risk to freshwater fish and amphibians, but may pose a risk to freshwater algae, freshwater plants, marine/estuarine invertebrates and marine fish if exposed to high enough concentrations. Hazard statements and mitigation measures (spray buffer zones) are required on product labels to protect aquatic organisms.

Glyphosate, AMPA and POEA do not meet all Toxic Substances Management Policy (TSMP) Track 1 criteria and are not considered Track 1 substances. Other than incident reports of damage to plants and one exceptional incident regarding fish in a river (PRVD2015-01, Section 4.2.3), there are currently no environmental incident reports involving glyphosate in Canada.

Value Considerations

What is the Value of Glyphosate?

Glyphosate plays an important role in Canadian weed management in both agricultural production and non-agricultural land management and is the most widely used herbicide in Canada.

Glyphosate is an important herbicide for Canadian agriculture:

- Due largely to its broad and flexible use pattern and its wide weed-control spectrum, it is the most widely used herbicide in several major crops grown in Canada, such as canola, soybean, field corn and wheat. It is also one of only a few herbicides regularly used in fruit orchards, such as apple.
- It is the essential herbicide for use on glyphosate tolerant crops (GTCs), including canola, soybean, corn, sweet corn and sugar beet. The combination of GTCs and glyphosate has been adopted as an important agricultural production practice in Canada.
- It has a wide application window ranging from pre-seeding to after seeding (prior to crop emergence), in-crop, pre-harvest or post-harvest, providing a flexible and effective weed management program.
- It is one of a few herbicides that can also be used as a harvest management and desiccation treatment.
- Post-harvest stubble treatment with glyphosate allows reduced or zero tillage, which has facilitated the adoption of conservation agriculture that results in improved soil quality.

Glyphosate is also an important weed management tool and is widely used for weed control in non-agricultural land management, such as forestry, industrial areas, and along rights-of-way. It is an effective tool for control of many invasive weed species and is also used in the control of toxic plants, such as poison ivy.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human health and the environment. These directions must be followed by law. As a result of the re-evaluation of glyphosate, the PMRA is requiring further risk-reduction measures in addition to those already listed on glyphosate product labels.

Additional risk-reduction measures are discussed below. Label amendments to be implemented are found in Appendix IV.

Human Health

- To protect commercial and residential applicators: glyphosate is not to be applied using hand-wicking or hand-daubing methods.
- To protect workers entering treated sites: a restricted-entry interval (REI) of 12 hours is required for agricultural uses.
- To protect bystanders: a statement is required indicating that the product is to be applied only when the potential for drift to areas of human habitation or areas of human activity, such as houses, cottages, schools and recreational areas, is minimal.

Environment

- Environmental hazard statements are added to inform users of toxicity to non-target species.
- Spray buffer zones to protect non-target terrestrial and aquatic habitats are required.
- To reduce the potential for runoff of glyphosate to adjacent aquatic habitats, precautionary statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecasted are required. In addition, a vegetative strip between the treatment area and the edge of a water body is recommended to reduce runoff of glyphosate to aquatic areas.

What Additional Scientific Information is Being Requested?

There are no additional data requirements proposed as a condition of continued registration of glyphosate products.

International Regulatory Status and Updates on Glyphosate

The PMRA routinely works collaboratively with other member countries within the Organisation for Economic Co-operation and Development (OECD) on the regulation of pesticides. As part of the re-evaluation of an active ingredient, the PMRA takes into consideration recent developments and new information on the status of a pesticide in other jurisdictions. Glyphosate is currently acceptable for use in other OECD countries, including the United States, Australia and the European Union. As of 8 March 2017, no decision by an OECD member country to prohibit all uses of glyphosate for health or environmental reasons has been identified.

In March, 2015, the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) published a summary of results of their hazard classification of five pesticides, including glyphosate. IARC classified glyphosate as probably carcinogenic to humans. It is important to note that the IARC classification is a hazard classification and not a health risk assessment. This means that the level of human exposure, which determines the actual risk, was not taken into account by IARC.

In November, 2015, the European Food Safety Authority (EFSA) finalized their re-assessment of glyphosate, concluding that glyphosate is unlikely to pose a carcinogenic hazard to humans. The EU also set an acute reference dose, which is the same as that set by the PMRA (PRVD2015-01). In May 2016, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) concluded that glyphosate is unlikely to be genotoxic at anticipated dietary exposures and that it is unlikely to pose a carcinogenic risk to humans from exposure through the diet. In March, 2017, the European Chemical Agency (ECHA) and the Australian Pesticides and Veterinary Medicines Authority (APVMA) released their determination that glyphosate is not a carcinogen. Currently, no pesticide regulatory authority, including Health Canada, considers glyphosate to be a carcinogenic risk of concern to humans.

Canada and the USEPA have been collaborating on the re-evaluation of glyphosate. In December 2016, the USEPA Scientific Advisory Panel (SAP) discussed the cancer potential of glyphosate, and Health Canada's PMRA participated as an observer. The final SAP meeting report was posted on March 17, 2017. The PMRA is continuing to monitor regulatory activities from other regulatory organizations, including the USEPA's review of the SAP recommendations and final determination regarding the potential carcinogenicity of glyphosate.

Health Canada's PMRA sets Maximum Residue Limits (MRLs) for pesticide residues on food, which is the maximum amount of residue that is expected to remain on food products when a pesticide is used according to label directions. These are set at levels well below the amount that could pose a health concern. In 2015, the Canadian Food Inspection Agency (CFIA) tested approximately 700 samples consisting of a variety of juice and juice blends, grains and grain products, beans, lentils, and a wide variety of fruit and vegetables. The CFIA also initiated a targeted survey of approximately 2,500 samples, looking at levels of glyphosate in bean, pea, lentil, chickpea and soy products, as well as less commonly consumed grains such as barley, buckwheat and quinoa. The results show a high degree of compliance with the MRLs established by the PMRA for glyphosate. The CFIA anticipates having the full analysis completed by Spring 2017.

Other Information

Any person may file a notice of objection regarding this decision on glyphosate within 60 days from the date of publication of Re-evaluation Decision RVD2017-01, *Glyphosate*. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of Health Canada's website (Request a Reconsideration of Decision), or contact the PMRA's Pest Management Information Service.

List of Abbreviations

AD	administered dose
ADI	allowable daily intake
a.e.	acid equivalent
AFC	antibody forming cells
AHS	agricultural health study
AMPA	aminomethylphosphonic acid
APVMA	Australian Pesticide and Veterinary Medicines Authority
ARfD	acute reference dose
ASAE	American Society of Agricultural Engineers
ATAE	phosphate ester, tallowamine, ethoxylated
Atm	atmosphere
BAF	bioaccumulation factor
BCF	bioconcentration factor
Bt	*Bacillus thuringiensis*
BVL	The German Federal Office for Consumer Protection and Food Safety
CARC	Cancer Assessment Review Committee
CAS	Chemical Abstracts Service
CFIA	Canadian Food Inspection Agency
CHMS	Canadian Health Measures Survey
Cm	centimeter
DACO	Data Code
DAR	Draft Assessment Report
DIR	Directive
DMTT	PMRA drift mitigation technical team
DT_{50}	time required for 50% dissipation of the initial concentration
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
ECx	effective concentration on x (any number) % of the population
ECHA	European Chemicals Agency
EDSP	Endocrine Disruptor Screening Program
EDSTAC	Endocrine Disruptor Screening and Testing Advisory Committee
EDTA	Endocrine Disrupters Testing and Assessment
EFSA	European Food Safety Authority
EP	end-use product
EU	European Union
EUP	end-use product
EUP + POEA	end-use products containing the surfactant POEA
EUP NO POEA	end-use products that do not contain POEA
FA	fraction of species affected
FAO	Food and Agriculture Organization of the United Nations
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
GLP	Good Laboratory Practices
GMO	genetically modified
Ha	hectare(s)

HC_5	hazardous concentration to five percent of species in a Species Sensitivity Distribution (SSD)
HD_5	hazardous dose to five percent of species in a Species Sensitivity Distribution (SSD)
Hr	hour(s)
HL	Hodgkin's lymphoma
IARC	International Agency for Research on Cancer
ICH	International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgM	Immunoglobulin M
IPA salt	isopropylamine salt
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
JGTF	Joint Glyphosate Task Force
JMPR	Joint WHO/FAO Meeting on Pesticide Residues
K_{ow}	*n*-octanol-water partition coefficient
L	litre
Lab	laboratory
LC_{50}	lethal concentration on 50% of the population
LC_x	lethal concentration on x (any number) % of the population
Log	logarithm
LOAEL	lowest observed adverse effect level
m^3	meter cube
mg	milligram
mm	millimeter
Mn	Manganese
MOA	Mode of Action
MOE	Margin of Exposure
MRL	Maximum Residue Limit
MWCF	Molecular Weight Conversion Factor
N. bruchi	*Neochetina bruchi*
Ng	nanogram
NHL	Non-Hodgkin Lymphoma
NOAEL	no observed adverse effect level
NOEC	no-observed-effect-concentration
NOEL	no-observed-effect-level
NOI	notice of intent
NPAFC	North Pacific Anadromous Fish Commission
NTP	National Toxicology Program
NZEPA	New Zealand Environmental Protection Authority
OECD	Organization for Economic Co-operation and Development
OPP	Office of Pesticides
Pa	pascal
PCPA	Pest Control Products Act
PMRA	Pest Management Regulatory Agency
POEA	Polyethoxylated tallow amines
PPE	Personal Protective Equipment
ppm	parts per million

PRVD	Proposed Re-evaluation Decision
RAR	Renewal Assessment Report
ROS	reactive oxygen species
RD	Residue Definition
RED	Reregistration Eligibility Decision
REG	Regulatory Note
REI	Restricted-Entry Interval
REV	Re-evaluation Note
RVD	Re-evaluation Decision
SAP	Scientific Advisory Panel
SPN	Science Policy Note
spp.	species (plural)
SSD	species sensitivity distribution
Tech.	technical
TGAI	technical grade active ingredient
TSMP	toxic substances management policy
TTR	Turf Transferable Residue
UK	United Kingdom
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
VMG	Validation Management Groups
WHO	World Health Organization

Appendix I Comments and Responses

The PMRA received written comments from the technical registrants, the public and other stakeholders relating to the *Proposed Re-evaluation Decision PRVD2015-01, Glyphosate*. The comments and PMRA responses are summarized based on common scientific themes.

1.0 Comments Related to the Health Risk Assessments

1.1 Comments Related to Toxicology

In addition to specific comments related to the toxicological evaluation of glyphosate, comments related to broader considerations, were also received. These broader comments included questions on the established paradigms for the toxicological evaluation of chemicals in general, comments on the Organization for Economic Co-operation and Development (OECD) guidelines for the testing of chemicals, concerns relating to the independence of the scientific findings, principles of Good Laboratory Practices (GLP), and other aspects of toxicological assessments. Although these broader types of comments were beyond the scope of the re-evaluation of glyphosate, every effort has been made to respond to the underlying concerns in the submitted comments as they relate to the toxicology review and health aspects of the glyphosate re-evaluation in Canada.

1.1.1 Salivary gland alterations and Acceptable Daily Intake (ADI)

Comment
The Joint Glyphosate Task Force (JGTF) proposed that the observation of cellular alterations in salivary glands results from oral irritation caused by dietary administration of glyphosate acid – a strong organic acid. New data was submitted to support this conclusion. In addition, it was noted that Canadian glyphosate formulations do not contain the technical acid, but instead contain neutral glyphosate salts (for example, potassium, ammonium, and isopropylamine). The JGTF requested that the PMRA consider the new data, re-assess the adversity of this finding, and base the ADI calculation on a more toxicologically relevant No Observed Adverse Effect Level (NOAEL).

PMRA Response
The newly submitted data consisted of a dose-range finding study and a non-guideline definitive study that examined the effects of citric acid administered to rats via gavage (to bypass direct oral exposure) or via diet, and trisodium citrate dihydrate given via diet for seven weeks. Rats treated with citric acid in their diet (a low pH diet) exhibited more pronounced changes in parotid glands (increased weight and histopathology severity) compared to rats receiving citric acid via gavage, or trisodium citrate dihydrate by diet (high pH diet).

However, an acidic diet did not appear to be the only factor responsible for changes in parotid glands, since these changes (albeit less pronounced) were also observed in both the high pH diet and gavage-treated citric acid (low pH) groups. Also, other organizations have conducted studies examining different modes of action (MOAs) that might explain changes observed in salivary glands of animals fed glyphosate-treated diets.

For example, as discussed in PRVD2015-01, (page 12), studies by the National Toxicology Program (NTP) indicated that glyphosate may be a β-adrenergic receptor agonist, as histological similarities were noted in salivary glands of animals treated with glyphosate acid, or a β-adrenergic receptor agonist (isoproterenol), and were reduced in severity by propranolol (a β-adrenergic receptor antagonist).

Additionally, the hazard assessment was based on the 'active substance' (glyphosate acid). Guideline toxicity data for "neutral" glyphosate salts, with particular attention to salivary gland examination in repeat-dose studies, were not available for selection of the toxicity endpoints.

The toxicological evaluation relied on a number of co-critical studies, rather than one 'key study', to establish each endpoint. The ADI (PRVD2015-01, page 20) is based on a 2-year study in rats with a NOAEL of 32/34 mg/kg bw/day, the highest (combined) NOAEL for all 2-year rat studies. The lowest (combined) Lowest Observed Adverse Effect Level (LOAEL) is 100 mg/kg bw/day, based on decreased body weight and increased incidences and severity of cellular alterations in the parotid and submandibular glands in one of the two-year rat studies. This choice of NOAEL and LOAEL is further supported by the NOAEL of 30 and LOAEL of 100 mg/kg bw/day, based on decreased body weight in three one-year dog studies. Thus, the selected ADI is based on two primary findings (decreased body weight as well as histological changes in the parotid salivary gland) observed in a number of different studies. No revision is required.

1.1.2 Acute Reference Dose (ARfD) for females 13-49 years of age

Comment
The endpoint selected for the ARfD for females 13-49 years of age was considered by the JGTF to be based on a spurious finding that is not reflected across developmental toxicity studies of glyphosate in rabbits. The JGTF presented an evaluation of seven rabbit developmental toxicity studies conducted by Kimmel et al. (2013), which concluded that the body of data failed to support an increased incidence of interventricular septal defects in the fetuses resulting from treatment with glyphosate during gestation in rabbits. Overall, the JGTF requested that the ARfD for this subpopulation be aligned with the ARfD for the general population.

PMRA Response
As noted in PRVD2015-01, the PMRA considered the evaluation conducted by Kimmel et al. (2013) in detail, as well as other available information, and based its conclusion on the overall weight-of-evidence in establishing an ARfD for the subpopulation of females 13-49 years of age.

Briefly, several limitations were noted in the analysis by Kimmel et al. (2013) including data tabulation errors and a lack of, or inadequately characterized, historical control data for key studies, including the study on which the PMRA based the ARfD. A re-analysis of this key study (Brooker et al. 1991, PMRA #1161779; PRVD2015-01) in conjunction with additional historical control data supplied by the JGTF resulted in the PMRA concluding that the incidence of cardiac malformations was increased relative to both concurrent and historical control data in high-dose animals, with an increase in variations at the mid-dose. The additional historical data provided by the JGTF did not alter the PMRA's original conclusions, thus, the ARfD for females 13-49 years of age was not revised.

1.1.3 Cancer Risk Assessment

Comments

1.1.3.1 International Agency for Research on Cancer (IARC) Glyphosate Monograph[5]

The majority of comments in relation to the 2015 IARC assessment, which classified glyphosate as 'probably carcinogenic to humans', requested that the PMRA review and re-assess the potential carcinogenicity of glyphosate, and restrict/ban its uses in Canada. Some comments noted that while the IARC assessment is a hazard classification, it also took into account the human exposure levels to glyphosate, largely by incorporating the epidemiological studies into the assessment. Some comments recommended that the PMRA apply the IARC classification in selecting a sensitive endpoint for occupational and bystander risk assessment in order to protect against the risk of developing non-Hodgkin's lymphoma and/or other cancers.

1.1.3.2 Ovarian Tubulostromal Tumours

The JGTF noted that PRVD2015-01 reported an increased incidence of ovarian tubulostromal tumours. The JGTF stated that these neoplasms arise out of the germinal epithelium of the ovarian stroma, are similar to those seen in epithelial hyperplasia, and therefore, do not provide sufficient evidence for oncogenicity. They also provided historical control data relevant to the strain of mice used, and noted that the reported incidence was within the range of Charles River historical control data for this finding. The JGTF requested that PMRA consider this finding as not related to glyphosate treatment and revise the text on page 89 of PRVD2015-01 from "equivocal evidence of oncogenicity" to "no evidence of oncogenicity"

1.1.3.3 Agricultural Health Study and Multiple Myeloma

The JGTF requested that the PMRA reconsider the suggested association between multiple myeloma and glyphosate use that was reported by the Agricultural Health Study (AHS) publication (De Roos et al. 2005, PMRA#:2391583). The comments indicated that it has been over 10 years since the study was conducted and a follow-up study, noted by De Roos as being necessary, has not been performed. The JGTF also noted that in an effort to understand how the conclusion of 'suggested association' was reached in the AHS study, the data were analyzed by a third-party expert (Sorahan, 2015) who determined that De Roos et. al., 2005 had pared down the AHS data set to come to the conclusion of 'suggested association'. When the full data set is analyzed, the risk ratio is 1.1, demonstrating no association between multiple myeloma and glyphosate use. Additionally, no association between multiple myeloma and glyphosate use was noted by the IARC review of glyphosate, which considered the Sorahan (2015) paper.

[5] IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 112 (2015). Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. Available online from http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf [last accessed June, 2016]

PMRA Response to Comments 1.1.3.1 – 1.1.3.3

Background

In March, 2015, the International Agency for Research on Cancer (IARC) published a summary of the basis for their hazard classifications of five pesticides, including glyphosate, which they classified as 'probably carcinogenic to humans'. The PMRA's position on the IARC's hazard-based classification was included in PRVD2015-01, published in April, 2015, however, the full IARC monograph only became available in July, 2015. The PMRA has since reviewed this document; a summary of the PMRA review is discussed below.

The IARC Assessment

The PMRA and IARC assessments of the carcinogenic potential of glyphosate were based on different datasets and considerations. As noted in Re-evaluation Note 2010 (REV2010-02), the PMRA collaborated with the United States Environmental Protection Agency (USEPA) on the re-evaluation of glyphosate, which included the examination of published scientific toxicity data according to the principles set out in USEPA guidance.[6] Additionally, considerations laid out in a second USEPA guidance[7] document were applied in the review of published epidemiology data.

The carcinogenic potential of glyphosate acid, the technical active ingredient, was assessed by the PMRA using a weight-of-evidence approach. Many registrant-supplied studies are available on the carcinogenic potential of glyphosate, which include lifetime cancer bioassays, as well as in vitro and in vivo mutagenicity studies. In addition, published data as well as epidemiological data were available for consideration. Results were then integrated and weighed according to their reliability, relevance and consistency. Note that studies conducted with glyphosate alone were considered more relevant in characterizing its inherent toxicity than were studies on the formulated products reported in the scientific literature, as the latter contained a variety of other constituents that, in most cases, were not identified. The compositions of formulated products are considered proprietary data, and often differ between countries. However, the composition of the formulated products must be disclosed to regulatory authorities in the country of registration; (see Genotoxicity section below). Although it is argued that formulated glyphosate products are more representative of 'real life' conditions, it is important to keep in mind that many different products (pesticide and non-pesticide) share many of these same constituents. In order to fully characterize a pesticide active ingredient, it is necessary to understand its inherent toxicity, which can only be characterized in the absence of these other constituents.

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6 EPA (U.S. Environmental Protection Agency), 2012, Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment. Available online from http://www2.epa.gov/sites/production/files/2015-07/documents/lit-studies.pdf [last accessed February, 2016]

7 EPA (U.S. Environmental Protection Agency), 2010, February 2010 FIFRA SAP meeting minutes: Draft Framework and Case studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment. Available online from https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0125-0079 [last accessed February 2016]

In addition, studies that complied with internationally accepted test guidelines were considered by the PMRA to be more relevant and reliable than published studies conducted with methodologies not recognized by regulatory agencies or organizations, such as the OECD. In total, the PMRA, in cooperation with the USEPA, assessed a much larger and more relevant body of scientific information than was considered by the IARC.

Conversely, in its evaluation of the carcinogenic potential of glyphosate, the IARC considered only published sources of toxicology data, which included the scientific literature and certain documents published by regulatory agencies. The IARC did not directly consider, or did not consider at all, unpublished toxicology studies that were available to international regulatory agencies. It is the PMRA's understanding that unpublished registrant-sponsored studies are not requested by the IARC for their deliberations. Furthermore, the IARC classifications of carcinogenic hazard are based on scientific consensus related to the evidence examined, but do not provide risk information or recommendations for regulation or legislation. The IARC assessment relied on many studies that did not characterize the composition of the tested mixtures (formulated products) and/or grouped all glyphosate formulated products, regardless of their composition. The composition of glyphosate formulated products differs around the world, even in those marketed under the same trade name. This difference in the evaluation approach used by the IARC and the PMRA is an important distinction because some studies, mostly in vitro, with glyphosate formulated products suggest that certain formulations are genotoxic, while studies examining the active substance alone do not show this effect. This may indicate that genotoxicity observed in these studies is related to other constituents in the formulated product rather than glyphosate acid. The constituents of all pest control products registered in Canada are disclosed to the PMRA, and toxicity data (as well as other data) are also required for each formulated product, which are examined during the pre-market review process.

Genotoxicity

The PMRA did not identify any genotoxic potential for the active ingredient glyphosate acid. Negative results for in vitro and in vivo gene mutation and chromosomal effect assays in mammalian cells contributed to the overall conclusion that the active ingredient glyphosate was not genotoxic. In vitro studies are generally conducted to predict a potential effect in animal (in vivo) studies. In vivo studies are weighted more than in vitro studies based on relevancy and integrated metabolism of the whole animal.

A large battery of genotoxicity assays conducted according to the OECD test guidelines for glyphosate is available. Many studies have been replicated several times, and all indicated negative results for genotoxicity. The IARC assessment did not consider the majority of these studies. Instead, the IARC monograph reported mixed results for studies with glyphosate formulated products that examined DNA damage, gene mutation, and chromosomal aberrations, and included results from non-mammalian systems – for example fish, and plants, that are not considered relevant for human health hazard characterization.

The IARC monograph also noted that in several cases, positive results occurred at very high or toxic dose levels only. It is important to characterize the relationship of genotoxic results in the context of observed cytotoxicity. Positive results at very high or toxic dose levels indicate that the genotoxic effects are due to cytotoxicity rather than direct DNA-acting properties of glyphosate formulated products. High-dose cytotoxicity was one factor in the weight-of-evidence

approach used by the PMRA when considering the genotoxic potential of glyphosate, and is consistent with international approaches (EFSA 2011,[8] USEPA 1986,[9] USFDA, ICH S2(R1)[10]). The observed cytotoxicity is likely associated with surfactants that are present in many formulated products. For example, polyethoxylated tallow amines (POEAs), which are typical surfactant components of many glyphosate products, were shown to produce cytotoxic effects such as perturbation/disruption of the mitochondrial membrane in cultured mammalian cells (Levine et al. 2007,[11] Kier and Kirkland 2013[12]). A number of negative genotoxicity studies were reported by Kier and Kirkland (2013), but not considered by the IARC. It should be noted that genotoxic effects resulting from cytotoxicity exhibit a threshold, and carefully selected reference doses protect against this effect.

The IARC suggested other 'mechanisms of action' that might contribute to potential carcinogenicity, such as inflammation, immunosuppression, endocrine disrupting activity and oxidative stress, which were based mainly on in vitro studies. However, no evidence of glyphosate-induced immunosuppression was observed in a registrant-supplied guideline immunotoxicity study reviewed by the PMRA. In addition, no other studies in the extensive toxicity database suggested a concern for immunotoxicity, inflammation or oxidative stress. Glyphosate also showed no evidence of interaction with estrogen, androgen or thyroid endocrine pathways in studies conducted by the USEPA Endocrine Disruptor Screening Program (EDSP).

Carcinogenicity

1. Studies in Animals

As reported in PRVD2015-01, the PMRA also assessed the carcinogenic potential of glyphosate in several long-term animal studies, which included two mouse studies and four rat studies, as well as studies in the published literature. Although, not all available carcinogenicity studies on glyphosate were submitted to the PMRA, reviews, evaluation reports, and committee meeting documents from international regulatory authorities (EFSA and USEPA) for these particular studies were considered by the PMRA. No evidence of carcinogenicity was identified in any of the rat studies reviewed by the PMRA, or in the additional rat studies reviewed by other regulatory authorities.

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8 EFSA (European Food Safety Authority), 2011. Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Scientific Committee, EFSA journal, 9, 2379

9 EPA (U.S. Environmental Protection Agency), 1986. Guidelines for mutagenicity risk assessment. Fed. Register 51. 34006-34012.

10 FDA (U.S. Food and Drug Administration), 2012. Guidance for Industry. S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use. Available online from http://www.fda.gov/downloads/Drugs/Guidances/ucm074931.pdf [last accessed February, 2016]

11 Levine SL, Han Z, Liu J, et al. (2007). Disrupting mitochondrial function with surfactants inhibits MA-10 Leydig cell steroidogenesis. Cell Biology and Toxicology, 23, 385–400. Available online from http://link.springer.com/article/10.1007%2Fs10565-007-9001-6 [last accessed June, 2016]

12 Larry D. Kier & David J. Kirkland (2013) Review of genotoxicity studies of glyphosate and glyphosate-based formulations, Critical Reviews in Toxicology, 43:4, 283-315. Available online from http://www.tandfonline.com/doi/full/10.3109/10408444.2013.770820#.V2G7ZtJIiUk [last accessed June, 2016]

The IARC assessed seven long term studies in rats and two studies in mice. Pancreatic islet cell adenomas were noted in male rats in two of the rat studies. However, these findings were not dose-related and/or occurred at the low dose only. The IARC also reported a statistically significant positive trend for hepatocellular adenomas in male rats only (with no evidence of pre-neoplastic lesions or progression to carcinomas), and a statistically significant positive trend for thyroid C-cell adenomas in female rats only. None of these tumours were reproduced in other chronic studies in rats.

PRVD2015-01 reported a marginal increase in the incidence of ovarian tubulostromal hyperplasia and adenomas in mice. However, since adenomas were observed at the limit dose of testing, they were not considered relevant for human health risk assessment. Furthermore, additional historical control data submitted during the PRVD comment period indicated that the incidence of ovarian adenomas was actually within the historical control range for the conducting laboratory, which increased the likelihood that these tumours were not treatment-related.

For the two mouse studies, the IARC identified a positive trend for renal tubule adenomas and carcinomas in male mice in one study, and a positive trend for hemangiosarcoma in males in the other study. However, these tumours were not reproduced in other mouse studies, which used similar and higher doses (1000-4000 mg/kg bw/day).

Since the publication of PRVD2015-01, a review by Greim et al. (2015[13]) of 14 long-term glyphosate toxicity/carcinogenicity studies in rodents included four additional studies in rats and three additional studies in mice, which were negative for carcinogenicity. These seven studies were not considered acceptable by the IARC due to insufficient reporting of the study methods and results by Greim et al. The PMRA had access to detailed information for these studies, which were considered acceptable for hazard characterization; and the USEPA and EFSA also considered these studies as part of their assessment of the carcinogenic potential of glyphosate.

2. Epidemiological Studies

The PMRA, USEPA and the European Food Safety Authority (EFSA[14]) have concluded that the currently available epidemiological database does not support a causal relationship between exposure to glyphosate and cancer outcomes.

A general discussion of pivotal epidemiology studies, as identified in the IARC assessment, is presented below.

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13 Helmut Greim, David Saltmiras, Volker Mostert & Christian Strupp, (2015), Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies, Critical Reviews in Toxicology, 45:3, 185-208. Available online from http://dx.doi.org/10.3109/10408444.2014.1003423 [last accessed June, 2016]

14 Ntzani EE, Chondrogiorgi M, Ntritsos G, Evangelou E, Tzoulaki I. Literature review on epidemiological studies linking exposure to pesticides and health effects. EFSA (European Food Safety Authority), EFSA supporting publication 2013:EN-497, 159 pp. Available online from http://www.efsa.europa.eu/en/supporting/pub/497e [Last accessed February, 2016]

Multiple Myeloma

As a part of a larger study known as the Agricultural Health Study (AHS), a prospective cohort study examined cancer incidence in pesticide applicators in Iowa and North Carolina. As described in PRVD2015-01, the most relevant finding in this study was a non-statistically significant association between multiple myeloma and glyphosate exposure. The relative risk was 1.1 when adjusted for age (95% CI, 0.5-2.4; 32 cases; only 20 cases reported exposure to glyphosate), but was 2.6 (95% CI, 0.7-9.4) when adjusted for multiple confounders (age, smoking, other pesticides, alcohol consumption, family history of cancer, and education). Evidence for an exposure-response trend by duration or intensity of pesticide use was not observed during the relatively short period (enrollment in the study was 1993-1997 to end of 2001) of follow-up (PMRA#:2391583). In a follow-up analysis of male participants in the same cohort, no correlation was observed between exposure to glyphosate and risk of a pre-malignant plasma disorder (monoclonal gammopathy of undetermined significance) that typically precedes the development of multiple myeloma (Landgren et al., 2009). In multiple re-analyses of the AHS data, including that of Sorahan (2015), no definitive association between glyphosate exposure and multiple myeloma was observed.

Non-Hodgkin lymphoma (NHL)

In many case-control studies, as reported by IARC, the USEPA and EFSA, some investigators observed a positive, but generally non-statistically significantly association between glyphosate use and NHL cases, while others reported no association. Variation in the quality of exposure assessment, study design and methods, in addition to a lack of available information on confounding variables may explain inconsistencies in the data. NHL is also not a specific disease, as mentioned by most authors of these studies, but consists of multiple types of lymphoma that are classified for convenience as not being Hodgkin's lymphoma. For example, multiple myeloma can also be considered a type of NHL; however, the data on multiple myeloma was analysed separately by the IARC, instead of considering it with NHL studies. The World Health Organization has dismissed the dichotomous classification of lymphomas as NHL/HL (Hodgkin's lymphoma); and 43 different types of lymphomas have been characterized (Berry 2010[15]). Proper classification of the disease (for example, the type of cancer) is important in epidemiology studies in order to adequately link it with the exposure to a chemical.

The interpretation of available epidemiological studies involving glyphosate is problematic due to a lack of adequate characterization of glyphosate exposures, the small number of cancer cases, and other confounding variables. For example, glyphosate exposure was analyzed with several other pesticides, exposure was generally based on questionnaires, classification of the type of cancer was not consistent, and the contribution of toxicity from formulants could not be assessed.

[15] Berry, C.L. 2010. Relativism, regulation and the dangers of indifferent science. The Sir Roy Cameron lecture of the Royal College of Pathologists. Toxicology 267 (2010) 7-13. Available online from http://www.sciencedirect.com/science/article/pii/S0300483X09005812?np=y [Last accessed February 2016]

Only once an association is plausibly established can criteria, (such as Bradford Hill) be considered to determine whether a causal relationship exists[16]. Without a causal relationship, epidemiology data cannot be used to establish references doses or occupational endpoints.

Finally, it is important to note that the experts convened by the IARC to assess the carcinogenic hazard of glyphosate concluded that there is limited evidence of glyphosate-related carcinogenicity in humans based on the available epidemiological studies. This conclusion is consistent with the limited utility of epidemiology studies in selecting reference doses to conduct a human health risk assessment for glyphosate.

While epidemiology data have inherent limitations, reported findings have the advantage of being directly based on human exposures and population responses. Because of these advantages, epidemiological studies may provide valuable information in the Adverse Outcome Pathway framework[17]. The PMRA continues to support the conduct of well-designed epidemiological studies where exposure conditions are well characterized.

Conclusion

Overall, the IARC concluded that the evidence of carcinogenicity was limited in humans but sufficient in animals. This conclusion was reached based on statistically increased incidences of tumour findings in four chronic studies in rodents (two in rats and two in mice), as well results from genotoxicity (mostly in vitro) assays using formulated products. However, the IARC did not reflect the lack of dose-response relationships or other contextual information (for example, background/ historical control data, cytotoxicity) in their decision.

Based on a weight-of-evidence analysis that utilized all available carcinogenicity studies in animals, together with other contextual information, the PMRA did not consider any of the observed tumours to be treatment-related. The main aspects of this weight-of-evidence analysis are highlighted below:

- A clear dose-response was not observed for any of the noted tumours
- The statistically significant findings via pairwise comparisons were weighed against the lack of dose-response relationships.
- The statistically significant positive trend was weighed against the lack of consistency across several relevant studies from a total of fourteen long term toxicity/carcinogenicity studies in rodents.
- Slightly increased tumour incidences at dose levels at or above the limit dose of testing (1000 mg/kg bw/day) were not considered relevant for human health risk assessment.

16 EPA (U.S. Environmental Protection Agency), 2010, February 2010 FIFRA SAP meeting minutes: Draft Framework and Case studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment. Available online from https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0125-0079 [last accessed February, 2016]

17 OECD, Organisation for Economic Co-operation and Development (OECD), 2012, Adverse Outcome Pathways, Molecular Screening and Toxicogenomincs. Available online from http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm [Last accessed February, 2016]

- Incidences fell within valid historical control data from the respective performing laboratories.
- There was a lack of pre-neoplastic lesions (for example, foci, hypertrophy, and hyperplasia) and/or other biologically plausible evidence (for example, mode of action data) to relate the noted tumours to glyphosate treatment.
- The weight-of-evidence from a wide range of assays, both in vitro and in vivo, that examined various endpoints such as gene mutation, chromosomal damage, DNA damage and repair, indicated no genotoxic concern for glyphosate.
- The currently available epidemiology evidence does not support a causal relationship between exposure to glyphosate and cancer outcomes.

The PMRA's determination on the carcinogenic potential of glyphosate is consistent with the most recent conclusions of other international regulatory authorities and intergovernmental organizations (USEPA CARC Report,[18] EFSA,[19] JMPR,[20] ECHA,[21] and NZEPA[22]), which concluded that glyphosate is unlikely to be genotoxic or carcinogenic. Therefore, the PMRA's conclusion with respect to the carcinogenicity of glyphosate acid, as outlined in PRVD2015-01, is unchanged.

1.1.4 Immunotoxicity

Comment
The JGTF noted that no statistically significant increase in T-cell dependent antibody response or total activity in the immunotoxicity study was observed. The JGTF requested that the statement regarding "evidence of immunotoxicity" be corrected to "no evidence of immunotoxicity." The JGTF also requested that additional wording be included to qualify PMRA's conclusion of "an altered function of the immune system could not be ruled out" to provide further context to PRVD2015-01.

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18 EPA (U.S Environmental Protection Agency), 2015, Cancer Assessment Document – Evaluation of the Carcinogenic Potential of Glyphosate. Final Report. Cancer Assessment Review Committee. Available online from http://src.bna.com/eAi [Last accessed June, 2016]

19 EFSA (European Food Safety Authority), 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA Journal 2015; 13(11):4302 [107 pp.] Available online from: https://www.efsa.europa.eu/en/efsajournal/pub/4302 [Last accessed June, 2016]

20 Pesticides Residues in Food, 2016. Special Session of the Joint FAO/WHO Meeting on Pesticide Residues – Report 2016. ISSN 2070-2515. FAO Plant Production and Protection Paper 227. Available online from http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/ [last accessed June, 2016]

21 ECHA (European Chemicals Agency). Public consultation on the harmonised classification and labelling proposal for Glyphosate. ECHA/NI/16/25. 2016. Available online from http://echa.europa.eu/view-article/-/journal_content/title/public-consultation-on-the-harmonised-classification-and-labelling-proposal-for-glyphosate [last accessed June, 2016]

22 NZEPA (New Zealand Environmental Protection Authority). Review of the Evidence Relating to Glyphosate and Carcinogenicity. 2016. Available online from http://www.epa.govt.nz/Publications/EPA_glyphosate_review.pdf [last accessed August, 2016]

PMRA Response

In the registrant-submitted immunotoxicity study, a dose-related increase in the T-cell dependent antibody response (IgM (Immunoglobulin M) AFC (Antibody Forming Cells)/10^6 spleen cells) was observed. The magnitude of increase was 10%, 18%, and 31% at 150, 449 and 1448 mg/kg bw/day, respectively, compared to the control group. The test guideline stated that a response of 800-1,000 IgM AFC/10^6 spleen cells should be noted in the negative control mice for the strain used in the AFC assay. Examination of individual animal data for T-cell dependent antibody response revealed that seven, six and eight animals in low, mid- and high dose groups, respectively, had a response higher than 1000 IgM AFC/10^6 spleen cells, compared to four animals in the control group, which indicated a treatment-related effect.

PRVD2015-01 also noted a dose-related increase in total spleen activity (IgM AFC/spleen x 10^3). The magnitude of increase for this effect was 13%, 50% and 54% @ 150, 449 and 1448 mg/kg bw/day, respectively, compared to the value of the vehicle control group. A non-dose-related increase in spleen cellularity (spleen cells $\times$ 10^7) of 20% and 10% in the mid- and high dose animals, respectively was noted. This increased immune response in the AFC assay was considered potentially treatment-related. However, immune effects were not observed in the rest of the toxicity database, and ultimately, this finding did not impact the risk assessment.

In summary, the PMRA examined trends (for example, dose-response relationships) as well as statistical significance in assessing the relevance of the above findings. Given that the variation (standard deviation) in the AFC assay data are generally large, key considerations other than statistical significance were important in developing an overall conclusion. The WHO (2012[23]) recommends considering unintended immune system stimulation as a noteworthy finding, but one that may be difficult to characterize or unambiguously define as adverse. Similarly, the USFDA (2002[24]) considers unintentional immunostimulation as a potentially adverse effect.

1.1.5 Aggregate Endpoint

Comment

A number of comments contested the endpoint selected by the PMRA for aggregate risk assessment, indicating that the NOAEL of 32/34 mg/kg bw/day from a 2-year rat study was inappropriate. The comments recommended that the endpoint be based on a NOAEL of 10 mg/kg bw/day due to an increased incidence of renal tubular dilation in F_{3b} offspring at the LOAEL in a three-generation reproduction toxicity study, as identified by the USEPA Integrated Risk Information System (IRIS).

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23 WHO (World Health Organization – International Programme on Chemical Safety), 2012. Guidance for Immunotoxicity Risk Assessment for Chemicals. Available online from http://www.inchem.org/documents/harmproj/harmproj/harmproj10.pdf [Last accessed June, 2016]

24 FDA (U.S Food and Drug Administration), 2012, Guidance for Industry – Immunotoxicology Evaluation of Investigational New Drugs. Available online from http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079239.pdf [last accessed June, 2016]

PMRA Response

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). An initial step in performing an aggregate risk assessment is to review all available toxicity data and to identify the most appropriate toxicological endpoints of concern and their associated parameters (such as dose, duration, and route).[25]

Since histological changes in the salivary glands were observed in many repeat-dose oral studies over various durations in two species (rats and mice), it was considered a common endpoint of concern for aggregate risk assessment (as indicated in PRVD2015-01, page 27), particularly for potential aggregate exposure from food, drinking water and residential scenarios. In addition, this was considered appropriate for all durations since the same effects were observed from very short term dosing (28-day) or chronic dosing (two-year) studies. In reconciling the dosing routes, it was indicated that dermal toxicity studies did not examine salivary glands histologically and repeat dose inhalation studies were not available. As such, effects on salivary glands are assumed to occur via inhalation or dermal routes in the absence of route-specific and convincing mode of action data to support route-specificity of these findings.

Furthermore, the reproduction study in which renal tubular dilation was noted in the F_{3b} offspring, was not considered acceptable due to many reporting limitations. It is also important to note that this finding was observed macroscopically in a few animals only, and was considered a spurious finding in the USEPA Office of Pesticides (OPP), JMPR and EFSA assessments. Additionally, this finding does not meet the criteria for determining an appropriate toxicology endpoint for aggregate risk assessment (SPN2003-04[26]). Therefore, the endpoint chosen for aggregate risk assessment in PRVD2015-01 remains unchanged.

1.1.6 Cumulative Risk Assessment

Comment

A number of submitted comments recommended that PMRA conduct an assessment of the cumulative effects of the glyphosate pest control product and other pest control products that have a common mechanism of toxicity.

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25 PMRA (Pest Management Regulatory Agency), 2003, General Principles for Performing Aggregate Exposure and Risk Assessments. Available online from http://www.hc-sc.gc.ca/cps-spc/alt_formats/pacrb-dgapcr/pdf/pubs/pest/pol-guide/spn/spn2003-04-eng.pdf [Last accessed February, 2016]

26 EPA (U.S. Environmental Protection Agency), 2001, General Principles for Performing Aggregate Exposure and Risk Assessments. Available online from http://www2.epa.gov/sites/production/files/2015-07/documents/aggregate.pdf [Last accessed February, 2016]

PMRA Response

The *Pest Control Products Act* requires that PMRA assess the cumulative effects of pesticides. A cumulative assessment evaluates the potential adverse health effects from being exposed to more than one pesticide at a time from the same pesticide "group". These groups are created based on a common toxic effect that occurs by the same or similar mechanism. Glyphosate acid does not appear to share a common mode of toxicity with other pesticides. As such it does not belong to a 'pesticide group' that requires assessment of cumulative effects.

For more information and/or a description of the steps taken to determine a pesticide "group" for assessment of cumulative effects, refer to SPN2001-01.[27]

1.1.7 The *Pest Control Products Act* (PCPA) Hazard Characterization

Comment

A number of comments recommended that the PMRA apply a 10-fold *Pest Control Products Act* factor for human health risk assessment, as required under the *Pest Control Products Act*. The comments indicated that there was evidence of sensitivity of infants and children to glyphosate in the studies discussed in PRVD2015-01. In two of the three reproduction toxicity studies, decreased body weight in rat pups was noted at non-maternally toxic doses. The PMRA was also referred to studies in the published literature that reported endocrine effects and toxicity in the young.

PMRA Response

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential pre- and postnatal toxicity.

As indicated in PRVD2015-01 (page 17) with respect to the completeness of the toxicity database of glyphosate, many available guideline and non-guideline studies have investigated the potential developmental, reproductive, and endocrine effects of glyphosate. Recently, the USEPA completed an assessment of the results of their Endocrine Disrupting Screening Program (EDSP) Tier I testing and concluded that glyphosate showed no evidence of interaction with estrogen, androgen or thyroid endocrine pathways (USEPA, 2015). It is important to note that studies required in the EDSP program are of higher quality and reliability than certain studies available in the published scientific literature, including the in vitro assays cited in the comments received on PRVD2015-01.

With respect to potential pre- and postnatal toxicity, the two-generation reproduction toxicity studies in rats provided no indication of increased sensitivity of the young. In these studies, although offspring toxicity typically consisted of decreased body weight at doses that did not

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[27] PMRA (Pest Management Regulatory Agency), 2001, Science Policy Notice (SPN2001-01) Guidance for Identifying Pesticides that have a Common Mechanism of Toxicity for Human Health Risk Assessment Available online from http://www.hc-sc.gc.ca/cps-spc/alt_formats/pacrb-dgapcr/pdf/pubs/pest/pol-guide/spn/spn2001-01-eng.pdf [Last accessed June 2016]

appear to produce maternal toxicity, it was noted that these same dose levels produced toxicity in adult animals in other studies available in the glyphosate database, (PRVD2015-01, pages 14, 17, 80, 81) lessening the level of concern for this finding. Additionally, the selected reference doses provide a sufficient margin (1000-fold) to the dose levels at which the pup bodyweights were affected.

In summary, based on the completeness of the database with respect to developmental and reproductive toxicity, the10-fold *Pest Control Products Act* factor was reduced to 1-fold for most populations. However, a 3-fold *Pest Control Products Act* factor was retained for the ARfD for females 13-49 years of age, for reasons discussed in PRVD2015-01 (page 17) and Section 1.1.2 of this document. For more information on the application of the *Pest Control Products Act* factor, please refer to SPN2008-01.[28]

1.1.8 General Comments on Health Effects and Toxicology Review

Comment
A number of comments from various stakeholder organizations (for example, Canadian Association of Agri-Retailers, the Canola Council of Canada, and Central Kootenay Invasive Species Society) acknowledged and supported the proposed re-evaluation decision on the health aspects of glyphosate. These comments emphasized the importance of a science-based approach in reviewing glyphosate and agreed with the proposed regulatory label changes.

PMRA Response

The PMRA re-evaluation drew upon a large, comprehensive body of scientific information that included data from registrants, published scientific studies, as well as information from other regulatory authorities, which formed the basis of its conclusions.

1.1.9 Glyphosate, GMOs (Genetically modified) and Health effects

Comment
A number of comments cited information from various non-governmental organizations or independent researchers, and requested that the PMRA use these sources of information as evidence for health risks of pest control products containing glyphosate in order to restrict or phase-out the uses of these products in Canada.

[28] PMRA (Pest Management Regulatory Agency), 2008, Science Policy Note (SPN2008-01): The Application of Uncertainty Factors and the *Pest Control Products Act* Factor in the Human Health Risk Assessment of Pesticide. Available online from http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/spn2008-01/index-eng.php [Last accessed June, 2016]

PMRA Response

As noted in previous responses, the PMRA conducted a weight-of-evidence assessment that considered all relevant, hazard/toxicity data for glyphosate, including data from registrants, published scientific studies, and information from other regulatory authorities. In the PMRA assessment, published scientific toxicity data was evaluated according to the principles set out in a published USEPA guidance document.[29]

In contrast, while the documents/websites cited in these comments attempted to consolidate a wide range of sources of information, some of these studies were of low quality and reliability due to significant reporting limitations, and/or did not utilize accepted study methodologies, while others were anecdotal in nature. Also, as discussed in response to comments 1.1.3.1-1.1.3.3, studies based on formulated products are considered less relevant to characterizing the potential inherent toxicity of glyphosate itself, due to multiple and often unidentified constituents. Thus, the submitted citations did not result in a change to the toxicity assessment for glyphosate. The studies cited in these comments that were considered by the PMRA are listed in the reference list section of this document.

1.1.10 Glyphosate and Modern Diseases (such as Autism, and Celiac Disease)

Comment

A number of comments cited published articles that link glyphosate to various health problems such as autism, and celiac disease (for example, Samsel and Seneff 2013[30]; 2015[31]), and requested that PMRA restrict and/or phase-out the uses of pest control products containing glyphosate based on health effects reported in these articles.

PMRA Response

Correlations do not provide sufficient evidence of causation. These articles report disease frequencies in specific regions over several time periods. Although correlations were reported, these were difficult to interpret, as it could not be determined whether the health outcomes preceded or followed glyphosate application. These articles also lacked sufficient detail regarding the strength, consistency and specificity of the noted correlations. For example, in regions where glyphosate applications were low, it was not clear if the health outcomes occurred at lower incidences compared to those of the regions where glyphosate applications were at higher levels. Overall, due to the lack of adequate information regarding the amount, route or duration of exposure; or the timing between exposure and the onset of the symptoms, an association and/or causality relationship could not be assessed.

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29 EPA (U.S. Environmental Protection Agency), 2012, Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment. Available online from http://www2.epa.gov/sites/production/files/2015-07/documents/lit-studies.pdf [last accessed February, 2016]

30 Samsel A, and Seneff S. 2013. Glyphosate's suppression of Cytochrome P450 enzymes and amino acid biosynthesis by the gut microbiome: pathways to modern diseases. Entropy. 15: 1416-1463.

31 Samsel A, and Seneff S. 2015. Glyphosate, pathways to modern diseases III: Manganese, neurological diseases, and associated pathologies. Surgical Neurology International. 6 (45).

1.1.11 Health Effects on the Gastrointestinal Tract and its Microbiome

Comment
A number of comments cited published articles that report an impact of glyphosate on the human intestinal microbiome, producing gastrointestinal effects which, some propose, may ultimately affect human health. Some comments noted that glyphosate is patented as an antibiotic, and requested information on the long term effects of ingesting glyphosate, on the human gut microbiome. Overall, the comments claimed that the PMRA did not address the implications of the chelation activity and antimicrobial properties of glyphosate.

PMRA Response

Glyphosate targets an amino acid synthesis pathway in plants that is shared by certain types of bacteria, but not humans. There is very little scientific evidence to support the claim that glyphosate has any direct impact on human gut microflora, or has any subsequent health effect. Several reports[32,33] postulate that environmental chemicals may potentially lead to changes in normal gut microbiota. However, information to date is based on in vitro studies, with in vivo evidence being very limited and inconclusive.

The reference doses established by the PMRA, and documented in PRVD2015-01, include consideration of clinical signs of toxicity on the gastrointestinal tract and are considered protective of potential effects on the gastrointestinal tract.

1.1.12 Endocrine Effects

Comment
A few comments referred the PMRA to articles that indicated glyphosate was an endocrine disruptor and requested that the PMRA use this evidence to phase-out pest control products containing glyphosate.

PMRA Response

The cited articles were generally studies that examined the effects of glyphosate formulations on a specific biochemical pathway in in vitro tests. These studies frequently did not provide test material composition.

The PMRA considered multiple lines of evidence from various toxicity studies in assessing the potential for glyphosate to affect endocrine systems. Studies conducted by the NTP, guideline two-generation reproduction toxicity studies, as well as studies conducted under the US EDSP

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32 Shehata AA, Shrödl W, Aldin AA, Hafez HM, Kürger M. 2013. The effect of glyphosate on potential pathogens and beneficial members of poultry microbiota in vitro. Current Microbiology 66(4): 350-358. Available online from http://link.springer.com/article/10.1007%2Fs00284-012-0277-2 [Last accessed June, 2016]

33 Dietert, RR. The Microbiome in early life: self-completion and microbiota protection as health priorities. Birth Defects Research (Part B) 101: 333-340 (2014). Available online from http://onlinelibrary.wiley.com/doi/10.1002/bdrb.21116/abstract [last accessed June, 2016]

program (United States Endocrine Disruptor Screening Program), were considered. Glyphosate has not been shown to interact with any specific endocrine pathway and has no physical / chemical properties or structural similarity to other chemicals that are known to interact with the endocrine system. Finally, as noted in response to comment 1.7, the USEPA completed a weight-of-evidence assessment on results obtained from the EDSP assays and concluded that glyphosate does not interact with estrogen, androgen, or thyroid pathways and that additional Tier 2 data was not triggered.

Thus, there is no compelling evidence to suggest that glyphosate has any significant adverse effect on endocrine-related pathways. See also response to comment 2.2.7.

1.1.13 Bioaccumulation

Comment
A few comments questioned whether glyphosate could accumulate in the body over time and how glyphosate is monitored to ensure levels do not go above acceptable limits that could cause health effects.

PMRA Response

No indication of glyphosate accumulation was reported in any of the toxicity studies, as summarized in PRVD2015-01. When animals received single or repeat doses (14 days), in each case, the administered dose (AD) was excreted within 7 days post-dosing and negligible levels (under 1% of AD) remained in the examined tissues. Overall, the metabolic studies indicated poor absorption from the gut, almost complete excretion, and very minor metabolism in animals. Published regulatory reports by EFSA and the USEPA confirm these results. In summary, glyphosate is not expected to accumulate in the body over time. Refer also to response 2.2.8.

1.1.14 Use of Independent Scientific Studies

Comment
A number of comments stated that the PMRA, in its review of glyphosate, appeared to consider only "seller sponsored science". The comments referred the PMRA to a number of published studies that link glyphosate to health effects. Overall, these comments emphasized support for the use of "third party" data in assessing the health effects and making the final re-evaluation decision for glyphosate, in lieu of manufacturer-supplied data.

PMRA Response

Regulatory authorities world-wide regard studies that are performed under conditions of good laboratory practices (GLP) and according to internationally agreed upon study designs, such as the OECD test guidelines, as the most reliable, reproducible, and scientifically sound. Studies conducted according to these guidelines are of sufficient statistical power to detect effects of concern, they investigate many potential endpoints of toxicological concern, and have detailed individual animal results that enable regulatory authorities to thoroughly evaluate and interpret the data in an independent manner. Adherence to these guidelines produces studies in which regulators have a high degree of confidence.

Studies conducted by academic laboratories often have lower statistical power due to the use of fewer animals, investigate far fewer toxicological endpoints, and lack sufficient detail in their published form. These limitations prevent regulatory authorities from performing an in-depth analysis of study results.

As discussed in PRVD2015-01, the re-evaluation took into account all relevant sources of toxicity data in order to evaluate the potential health effects of glyphosate acid. This included an independent review of registrant-supplied data, which are required for the pesticide review and approval process in Canada, as well as consideration of scientific publications and information from other regulatory authorities.

For more information on the toxicology data requirements for registration of pest control products in Canada, please consult Guidance for Developing Datasets for Conventional Pest Control Product Applications: Data Codes for Parts 1 - 7 and 10[34] and/or 'OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring'.[35] Refer also to comment 2.2.9.

1.1.15 Health Effects of the Glyphosate Formulated Products

Comment

A number of comments questioned why glyphosate formulated products were not assessed for their health effects, stating that the health effects discussed in PRVD2015-01 were based on the active substance (glyphosate acid).

PMRA Response

Although the majority of mammalian toxicity studies for glyphosate were conducted using the active substance (glyphosate acid), toxicology studies that assess the acute hazard of formulated products are also examined. Individual formulated products are also used for other studies, such as in the generation of residue chemistry (field trial) data considered during the risk assessment phase. For more information on the data required for the active ingredient and formulated end use products for the registration of pest control products in Canada, please consult Guidance for Developing Datasets for Conventional Pest Control Product Applications: Data Codes for Parts 1-7 and 10.

In addition, as part of the glyphosate re-evaluation, an assessment was conducted on polyethoxylated tallow amines (POEA), which are a family of compounds often used as formulants in pest control products that function as surfactants. POEA substances (CAS no.

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34 Guidance for Developing Datasets for Conventional Pest Control Product Applications: Data Codes for Parts 1, 2, 3, 4, 5, 6, 7 and 10. Available online from http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/data-guide-donnees/index-eng.php [Last accessed Dec, 2016]

35 OECD (Organisation for Economic Co-operation and Development), 1997, OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring – Number 1. OECD Principles on Good Laboratory Practice (as revised in 1997). Available online from http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem(98)17&doclanguage=en [Last accessed June, 2016]

61791-26-2) are included on List 4B of PMRA's list of Formulants (see REG2005-01[36] page 28). Currently, formulants are categorized into one of the five lists which rank them in descending order of concern. List 4B contains formulants are of minimal concern under specific conditions of use. For more details on the regulation of formulants in pest control products, refer to the PMRA Regulatory Directive DIR2006-02.[37]

As indicated in PRVD2015-01, the USEPA completed a human health risk assessment for phosphate ester, tallowamine, ethoxylated (ATAE), which is a subfamily of POEA. The PMRA considered the USEPA review, and reviewed the available toxicity studies that made up the USEPA assessment, including the pivotal study used in endpoint selection, which was a combined repeat-dose rat toxicity study with a reproduction/developmental toxicity screening component. As noted in the USEPA assessment, glyphosate products that contain no more that 20% POEA by weight are not of concern. Currently, all registered glyphosate products in Canada meet this limit.

1.2 Comments Related to Occupational / Residential Exposure

1.2.1 Bystanders

Comment
There were many general comments suggesting that the current level of non-dietary exposure to glyphosate is not safe for the general public (bystanders).

PMRA Response
Only those uses where human exposure to a pesticide is well below the level that cause effects in animal tests are considered acceptable for registration in Canada. This was confirmed with the re-evaluation of glyphosate

During the re-evaluation of glyphosate, it was recognized that there is potential for short-term exposure when entering treated non-cropland areas (in other words, hiking through forests or parks that have recently been treated with glyphosate). Calculated MOEs for all lifestages met the target MOE and are therefore not of concern to human health. In the interest of promoting best management practices and to minimize human exposure the following label statement is required:

"Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings."

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36 PMRA (Pest Management Regulatory Agency), 2005. Regulatory Note: *PMRA List of Formulants*. Available online from http://publications.gc.ca/collections/Collection/H113-7-2005-1E.pdf [Last accessed February 2016]

37 PMRA (Pest Management Regulatory Agency), 2006. Regulatory Directive: *Formulants Policy and Implementation Guidance Document*. Available online from http://www.hc-sc.gc.ca/cps-spc/alt_formats/pacrb-dgapcr/pdf/pubs/pest/pol-guide/dir/dir2006-02-eng.pdf [Last accessed February, 2016]

1.2.2 Restricted-Entry Interval

Comment
Comments questioned the basis for changing the "Restricted-Entry Interval" to 12 hours for commercial class products, when PRVD2015-01 states that postapplication risks are not of concern for all uses. Comments indicated that, in general, glyphosate dries on the plant very quickly and there are no residues that can be readily passed on to workers. It was recommended that the label not specify a time limit but should instead indicate that field entry is allowed once the herbicide application has dried.

PMRA Response
A restricted-entry interval (REI) is the period of time that agricultural workers, or anyone else, must not do hand labor in treated areas after a pesticide has been applied. This is to allow residues and vapours to dissipate to safe levels for work to be performed. Hand labour tasks involve substantial worker contact with treated surfaces such as plants, plant parts, or soil.

All pest control products with agricultural uses require a minimum REI of 12 hours to protect workers, and others, from potential risks that may occur from both immediate and longer-term exposures to pesticide residues, vapors, and particulates. A minimum 12-hour REI allows residues to dry and vapors to dissipate, limiting potential effects such as irritation or allergic reactions.

1.2.3 Personal Protective Equipment

Comment
It was noted that in the proposed label amendments for products containing glyphosate, as presented in Appendix XII of PRVD2015-01, there is no mention of proposed changes for protective clothing at the time of mixing and loading, application, clean-up and repair. For commercial formulations of glyphosate, the current label wording makes no requirement for use of personal protective equipment during application. The lack of proposed label changes for protective clothing is an important oversight, especially the lack of requirement for protective clothing during spraying.

PMRA Response
The exposure estimates for mixers, loaders, and applicators of glyphosate used in the agricultural exposure assessment presented in PRVD2015-01 were based on a baseline level of PPE (long pants, long sleeved shirts and chemical-resistant gloves). The calculated dermal, inhalation, and combined MOEs are greater than the target MOE for all mixing, loading, and applying activities and therefore are not of concern. As such, no additional requirements for protective clothing beyond the baseline level of PPE are needed, as the existing labels already include the appropriate PPE.

1.2.4 Application Rates in Aggregate Exposure Assessment

Comment
In PRVD2015-01, all three aggregate exposure scenarios initially assumed 2 applications with a 7 day interval at the highest rate. At that application rate, the calculated MOEs for adult and youth/children (6 to <11 years old) scenarios reached the target MOE of 100, but the MOE for

children (1 to <2 years old) for the post-application + incidental oral exposure + chronic dietary scenario did not. It was interpreted that the PMRA changed the aggregate assessment to one application of glyphosate with a seven-day time-weighted turf transferable residue average for the entire aggregate assessment for all populations. It was suggested to use the highest application rate and frequency of glyphosate use to assess the aggregate exposures, and, if safety margins (MOE) were not met, to propose meaningful and wide-ranging use restrictions to increase human health protection.

PMRA Response
When conducting the aggregate exposure assessment, 2 applications (with a 7 day interval) at the highest rate were assumed. All calculated MOEs reached the target MOE except for children (1 to <2 years old) for the post-application + incidental oral exposure + chronic dietary scenario. Therefore, dietary and non-dietary exposure refinements were required.

The dietary exposure assessment used US Tolerances or Codex MRLs for situations where these values were greater than Canadian MRLs. However, domestic production and import statistics indicated that barley, oats, and wheat consumed in Canada are almost totally produced in Canada (>99%), with <1% imported. Thus, it was considered reasonable to use Canadian MRLs for these crops as a refinement in the calculation of the chronic dietary exposure estimates for the purpose of aggregation with residential exposure only, rather than the US and Codex group tolerance of 30 ppm. The current Canadian MRLs in these cereal crops are as follows: barley (and barley flour) - 10 ppm, barley milling fractions (except flour) -15 ppm, oat (and oat flour) - 15 ppm, oat milling fractions (except flour) - 35 ppm, wheat (and wheat flour) - 5 ppm, and wheat milling fraction (except flour) - 15 ppm.

In addition, assuming 2 applications (with a 7 day interval) at the maximum application rate is a highly conservative exposure assumption, as it is unlikely that children would be exposed to turf residues of the highest rate, at the lowest interval of application immediately after application. Therefore, a refinement using 1 application of glyphosate along with a 7 day time-weighted TTR average was used (the average resides of glyphosate were calculated over a 7 day span) for the entire aggregate assessment for all populations.

These refinements are health protective and all calculated MOEs met the target MOE and are not of concern to human health.

1.3 Comments Related to Dietary Exposure

1.3.1 Genetically Modified Crops

Comment
A number of comments expressed concern regarding the potential for higher residue levels of glyphosate in genetically modified (GM) crops, as reported in the article "*Compositional differences in soybeans on the market: glyphosate accumulates in Roundup Ready GM Soybeans. Bohn, T. et al., Food Chem. 2014, 153: 207-215.*"

PMRA Response

The residue chemistry of glyphosate, i.e. the nature and magnitude of residues of glyphosate in conventional (non-GM) crops, as well as in GM crops, is well understood and extensively documented. PMRA has received and reviewed all the metabolism studies required as per the PMRA Residue Chemistry Guidelines (Dir98-02[38]). The residue definition (RD) in plant commodities is based on scientifically sound metabolism studies conducted specifically in both types of crops. Whenever a new variant of GM crop is introduced on the market, the residue definition is reassessed based on mandatory supporting metabolism studies in that particular GM crop variant. The residue definition in animal commodities (resulting from feeding of the GM crop) is adjusted accordingly.

Currently there are three types of soybeans on the market: conventional (non-GM) soybean, EPSPS-GM soybean (containing the EPSPS gene) and GAT-GM soybean (containing the GAT gene). Based on metabolism studies in the respective crops, the RD in conventional and EPSPS soybeans are defined as the sum of glyphosate and its metabolite aminomethylphosphonic acid (AMPA). The RD in GAT soybean includes additional metabolites (acetylated glyphosate and acetylated AMPA) resulting from the specific biotransformation of glyphosate in GAT crops. As soybeans sold on the market cannot be distinguished with regards to whether they are conventional, EPSPS or GAT soybeans, the PMRA uses the most inclusive RD for soybeans, i.e., the RD in soybeans is the sum of glyphosate, AMPA and their acetylated counterparts.

All the metabolites included in the RD were deemed toxicologically equivalent to glyphosate. Consequently, in terms of residues, all the metabolites are expressed as the stoichiometric equivalent of glyphosate by using the appropriate molecular weight conversion factor (MWCF). The MWCFs are 1.5 for AMPA, 1.1 for N-acetyl AMPA and 0.8 for N-acetyl glyphosate. This means that the residue of glyphosate in soybeans (and in canola and corn comprising similar GM variants) is calculated as the sum: glyphosate + 1.5 AMPA + 1.1 N-acetyl AMPA + 0.8 N-acetyl glyphosate.

Residues of glyphosate (or any pesticide) in soybeans (or any crop) is a function of the agricultural practice by which they have been produced. GM soybeans are expected to have residue detects due to repeated spraying (in compliance with label directions) of plants throughout the production season. Conventional soybeans will contain lower residues levels because glyphosate is applied to weeds (before planting) and not on soybean plants. These facts are supported by field trial residue studies, which, as noted above, are required as per the PMRA Residue Chemistry Guidelines (Dir98-02). The field trial studies are conducted according to the petitioned-for use pattern and usage conditions (good agricultural practices) and constitute the basis for the registration and establishment of Maximum Residue Limits (MRLs). MRLs are established on the basis of worse case scenarios (maximum application rate, highest frequency of applications and shortest pre-harvest interval) within the agricultural practices. An MRL represents the maximum amount of residues that may remain on food when a pesticide is used according to label directions, and serves as a food safety standard. The results presented in the cited article did not exceed the established MRL of 20 mg/kg (20 ppm) for glyphosate in soybeans and confirm that current Canadian MRLs of glyphosate (including the metabolites) in

[38] PMRA (Pest Management Regulatory Agency), 1998. Regulatory Directive: *Residue Chemistry Guidelines*. Can be requested online from http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/dir98-02/index-eng.php [Last accessed August 2016]

soybeans are adequate. These MRLs were used in the estimation of short term (acute) as well as long term (chronic) dietary exposures. No dietary risk concerns were identified, as the levels of exposure estimates were well below the reference doses set for dietary risk assessment (the ARfD and ADI).

1.3.2 Mitigation Measures

Comment
A question was raised regarding a general (introductory) statement in Section 3.2 of PRVD2015-01 (Dietary Exposure and Risk Assessment) which reads: "*In situations where the need to mitigate dietary exposure has been identified, the following options are considered. Dietary exposure from Canadian agricultural uses can be mitigated through changes in the use pattern.*" The comment indicated that this statement implies that there are concerns with the glyphosate use pattern and, therefore, requested clarity on what mitigation measures were proposed.

PMRA Response
This is a general statement which would apply to any pesticide presenting dietary risk concerns. As no dietary risk concerns were identified for glyphosate, no mitigation measures were required.

1.3.3 Food Labelling

Comment
A comment requested that "glyphosate content" be added to all food labels (in grocery stores) so that consumers could decide whether they want to buy food containing glyphosate residues or not.

PMRA Response
Although Health Canada and the Canadian Food Inspection Agency (CFIA) share the responsibility for food labelling policies under the *Food and Drugs Act*, food labelling does not fall within the mandate of the PMRA or the *Pest Control Products Act* (PCPA). Other areas of Health Canada are responsible for developing policy and setting standards related to the health and safety aspects of labelling under the *Food and Drugs Act and Regulations*, whereas the CFIA applies these policies and enforces the regulations. The CFIA also has the mandate to develop general food labelling policies and regulations not related to health and safety. In particular, the CFIA is responsible for protecting consumers from misrepresentation and fraud with respect to food labelling, packaging and advertising, and for prescribing basic food labelling and advertising requirements.

With respect to glyphosate residues in foods, the CFIA is responsible for monitoring the Canadian food supply for pesticide residues and the determination of compliance with MRLs specified by Health Canada. In addition, both Canadian and international producers are aware of these MRLs and must comply with them in order to sell their produce in Canada or export to other countries that also have MRLs established. Therefore, it is expected that foods with residues higher than the MRL would not be present in the Canadian food supply.

For more details, please visit the CFIA Website at http://www.inspection.gc.ca/food/labelling/food-labelling-for-industry/method-of-production-claims/genetically-engineered-foods/eng/1333373177199/1333373638071

1.3.4 Glyphosate Used as Desiccant and Residue

Comment
Comments expressed concern about the use of glyphosate for pre-harvest desiccation on conventional crops, the level of residues left on desiccated crops at harvest and the resulting long-term dietary exposure.

PMRA Response
Glyphosate is registered for pre-harvest use (desiccation) on a number of conventional crops including wheat, barley, oats, canola, flax, lentils, peas, dry beans, and soybeans. To support this use, field trial residue studies were required to determine the level of residues resulting from the pre-harvest desiccation conducted according to the requested use pattern. Maximum residue limits (MRLs) for these crops were established on the basis of the submitted studies. Those MRLs were included in the estimation of short term (acute) as well as long term (chronic) dietary exposures. During PMRA's assessment, no dietary risk concerns were identified, as the levels of exposure estimates were well below the reference doses set for dietary risk assessment (the ARfD and ADI).

1.3.5 Safety of GMO Crops

Comment
There were general questions as to whether GM crops are safe for human consumption.

PMRA Response
Health Canada conducts a rigorous and thorough science-based assessment of all GM food products before they are allowed to enter the Canadian marketplace. The assessments are conducted under the *Food and Drug Regulations*, which prohibit manufacturers of these products from selling them in Canada until Health Canada has completed a full safety assessment and has found them to be as safe and nutritious as conventional foods.

The approach taken by Health Canada in the safety assessment of GM foods is based upon scientific principles developed through expert international consultation over the last twenty years with agencies such as the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the Organization for Economic Co-operation and Development (OECD). This same approach is currently applied by regulatory authorities around the world in countries such as the European Union, Australia/New Zealand, Japan and the United States. For more details, please visit the Health Canada Website at http://www.hc-sc.gc.ca/fn-an/gmf-agm/index-eng.php.

1.3.6 Acceptable Level of Exposure

Comment
Comments included the question: "What is considered as acceptable level of exposure and how is that monitored to be sure that levels do not become unacceptable?"

PMRA Response
When assessing pesticide related health risks, two key factors are considered: the dose levels at which no health effects occur in animal testing (basis for the establishment of toxicological reference doses for humans) and the levels to which people may be exposed through diet, when handling and applying the pesticide, or by entering treated sites (in other words, level of exposure). The dose levels used to assess risks (in other words, toxicological reference doses) are established to protect the most sensitive human population (for example, children and nursing mothers). Only pesticide uses for which the level of exposure (through diet for example) is well below levels that cause no effects in animal testing are considered acceptable for registration.

Reference doses define levels to which an individual can be exposed to a pesticide residue over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (also known as acceptable daily intake).

The amount of pesticide to which an individual is exposed (in other words, exposure) is determined by determining the amount of pesticide that is in or on the food (in other words, residue levels) and combining that with the amount and type of foods that people eat (in other words, food consumption). Risk is then estimated by comparing the level of exposure to the reference doses described above. As previously noted, if the estimated intake is less than the reference dose, there are no dietary risks of concern.

In addition, inherent to pesticide registration is the establishment of maximum residue limits (MRLs) of the pesticide in/on foods on which the pesticide has been applied. An MRL represents the maximum amount of residues that may remain on food when a pesticide is used according to label directions, and serves as a food safety standard. The MRLs are calculated from residue data obtained from field trials that are conducted using the maximum application rate and the shortest pre-harvest interval. These MRLs, or field trial residue values, are used to estimate the level of dietary exposure at the time of pesticide registration. A pesticide is registered only if the calculated level of exposure is acceptable (in other words, exposure does not exceed the toxicological reference dose). The Canadian Food Inspection Agency (CFIA) is responsible for monitoring the Canadian food supply for pesticide residues and work very closely with Health Canada (PMRA) to ensure that the foods available on the Canadian market are compliant with the MRLs. In 2015, the Canadian Food Inspection Agency (CFIA) tested approximately 700 samples consisting of a variety of juice and juice blends, grains and grain products, beans, lentils, and a wide variety of fruit and vegetables. The CFIA also initiated a targeted survey of approximately 2,500 samples, looking at levels of glyphosate in bean, pea, lentil, chickpea and soy products, as well as less commonly consumed grains such as barley, buckwheat and quinoa. The results show a high degree of compliance with the MRLs established by the PMRA for glyphosate. The CFIA anticipates having their full analysis completed by Spring 2017.

1.3.7 Monitoring of Glyphosate Residue

Comment
Several comments noted: 1) the necessity to monitor amounts of glyphosate applied on fields, especially where resistant weeds have emerged; 2) the necessity to measure glyphosate residues resulting from ordinary field applications (field trial residue data); 3) the necessity to obtain glyphosate residue data that are reflective of foods as consumed through monitoring programs in

which food samples down the chain of commerce are sampled and analysed; 4) further information on maximum residue levels of glyphosate in food; and 5) the necessity to monitor glyphosate residues in body fluids and tissues (biomonitoring); as they are not included in the *Third Report on Biomonitoring of Environmental Chemicals in Canada*.

PMRA Response

As noted in response to comment 1.3.6, glyphosate residues on foods have been measured in field trial studies that are required to register a pesticide for specific uses, as per PMRA Residue Chemistry Guidelines (Dir98-02). These field trial data were used for the establishment of maximum residue limits (MRLs) for glyphosate, that is, the maximum legally allowed amount of glyphosate residue that may remain on foods when glyphosate is used according to label directions. The MRLs are enforced by law, and, the conditions of registration must be observed in all circumstances, regardless of whether resistant weeds have emerged or not. In cases of weed resistance, a higher rate than what is currently on the labels cannot be used, as this could lead to MRL exceedance and would be in violation of the *Food and Drugs Act*. The *Food and Drugs Act* prohibits the sale of adulterated food; that is, food containing a pesticide residue that exceeds the specified MRL.

The Canadian Food Inspection Agency (CFIA) is responsible for monitoring the Canadian food supply for pesticide residues and the determination of compliance with MRLs specified by Health Canada. As noted in response to comment 1.3.6, in 2015, the Canadian Food Inspection Agency (CFIA) tested approximately 700 samples consisting of a variety of juice and juice blends, grains and grain products, beans, lentils, and a wide variety of fruit and vegetables. The CFIA also initiated a targeted survey of approximately 2,500 samples, looking at levels of glyphosate in bean, pea, lentil, chickpea and soy products, as well as less commonly consumed grains such as barley, buckwheat and quinoa. The results show a high degree of compliance with the MRLs established by the PMRA for glyphosate. The CFIA anticipates having the full analysis completed by spring 2017. A complete list of MRLs specified in Canada can be found on the PMRA's MRL Database, an online query application that allows users to search for specified MRLs, regulated under the *Pest Control Products Act*, for pesticides, including glyphosate, or food commodities (http://pr-rp.hc-sc.gc.ca/mrl-lrm/index-eng.php). For details on CFIA's monitoring program, please visit the CFIA website at http://www.inspection.gc.ca/food/fresh-fruits-and-vegetables/food-safety/chemical-residues/overview/eng/1374514433922/1374514696857.

Biomonitoring is a key tool used as an indicator and quantitative measure of exposure to chemicals in the environment. Human biomonitoring data contribute to our understanding of exposure and provide information to inform the management of the health risks posed by chemicals. The Canadian Health Measures Survey (CHMS) is an ongoing national biomonitoring survey led by Statistics Canada, in partnership with Health Canada and the Public Health Agency of Canada. Biomonitoring data have been reported for Cycle 1 (2007-2009), Cycle 2 (2009-2011) and Cycle 3 (2012-2013). Cycle 4 is currently underway, with data collection for this cycle having taken place from 2014 to 2015. These cycles are complementary, meaning that not all environmental chemicals (including pesticides) are included in a given cycle. For example, 55% of the chemicals measured in Cycle 2 were not included in Cycle 1 and about 31% of the chemicals measured in Cycle 3 were not included in previous cycles. Specific chemicals/pesticides are added to the list of measured chemicals in different cycles. Glyphosate, like many other pesticides, is being considered for inclusion in forthcoming cycles. For details on

the Canadian Health Measures Survey, please visit the Health Canada Website at http://www.hc-sc.gc.ca/ewh-semt/contaminants/human-humaine/chms-ecms-eng.php.

1.3.8 Glyphosate Use on Forest Vegetation and Effect on Health

Comment
One Aboriginal group provided the following comments:

I. Health Canada's glyphosate PRVD is based on dietary and occupational exposures that do not correspond with Anishinabek use of the territories for food, medicine and water;

II. Laboratory toxicological studies are based on reference values that do not conform to their own standards of risk, and do not take into account the cumulative effects of the environmental contaminants to which they are exposed;

III. They are concerned about the combined toxicity of glyphosate and the surfactants, solvents, and other additives.

PMRA Response
While the dietary risk assessment conducted by the PMRA does not directly assess the anticipated residues of glyphosate in edible forest vegetation, nor is the dietary burden to wild game specifically determined, based on assessments available, the PMRA does not expect that glyphosate residues from these foods would be of concern when ingested. This is because, in the dietary assessment that was conducted, residues in farm animal commodities were estimated and maximum residue limits (MRLs) were established by assuming the worst case scenario where the animal diet is considered to be comprised of 100% glyphosate-treated feedstuff, treated at the maximum application rate. This results in high-end residue estimates. For the same reason, residues in/on edible forest vegetation are expected to be low compared to MRLs established on conventional crops. These MRLs are established based on the worst case scenario, in other words, maximum application rate, shortest preharvest interval and maximum allowed number of applications per season. As noted in PRVD2015-01, using the above scenarios, there were no risk concerns from dietary exposure to glyphosate. The acute dietary exposure estimate (from food and drinking water) at the 95th percentile was 31% of the acute reference dose (ARfD) for females 13-49 years of age and ranged from 12% to 45% of the ARfD for all other population subgroups. The chronic dietary exposure estimate for the general population was 30% of the acceptable daily intake (ADI). Exposure estimates for population subgroups ranged from 20% of the ADI (for adults aged 50 years or older) to 70% of the ADI (for children 1-2 years old). Exposures less than 100% of the ARfD and ADI are not of concern. In the case of glyphosate, even when high-end (worst case) exposure estimates were used, no risk concerns to human health were identified.

The PMRA also conducted a health risk assessment for hikers walking through the forest immediately after application. The populations considered were adults, youths and children aged 6 to 10 years. From these estimates, no risk concerns were identified. As well, when exposures were aggregated (in other words, dietary exposure including from drinking water + non-dietary exposures as would occur from hiking in the forest), risks were also not of concern for the various population groups. Refer also to responses on environmental risk in Sections 2.2 and 2.4.

Regarding the cumulative effects of pesticides, please refer to the response to comments in Section comment 1.1.6 Cumulative Risk Assessment.

Regarding the combined toxicity of glyphosate and the surfactants, solvents and other additives, please refer to the response to comments in Section 1.1.15 Health Effects of the Glyphosate Formulated Products.

2.0 Comments Related to the Environmental Risk Assessments

2.1 Environmental Fate

2.1.1 Surficial and groundwater pollution and monitoring

Comment
Comments suggested or were concerned that glyphosate has the potential to leach to groundwater and natural areas, polluting water.

PMRA Response
In soil and water, glyphosate has been shown to break down quickly to aminomethylphosphonic acid (AMPA) through microbial processes and is considered to be non-persistent to moderately persistent. Glyphosate has low mobility in soil, giving it a low potential to contaminate groundwater systems, especially aquifers with low water hardness (Jayasumana et al. 2014). Glyphosate can enter surface waters when applied near water bodies or when carried in runoff, such as during a rain event on a steep slope. Glyphosate (without surfactant) and AMPA have comparable toxicological and ecotoxicological profiles, with both being considered to have low toxicity in general. According to the WHO (2004), the presence of glyphosate and AMPA at levels expected to be found in drinking water does not pose a risk to human health. Monitoring studies conducted throughout Canada indicate that glyphosate is rarely detected in groundwater. Although glyphosate is often detected in surface water, the concentrations detected are at relatively low levels that do not pose a risk of concern.

2.1.2 Glyphosate and AMPA persistence in soils and waters

Comment
Comments noted that glyphosate soil half-life values vary widely in terrestrial field dissipation studies in North America and that it may be more persistent than previously thought. Glyphosate may build up in soils and long-term negative effects are expected to occur. Glyphosate and AMPA are both frequently detected in soil and water in field dissipation studies from the United States (Battaglin et al. 2014).

PMRA Response
Glyphosate use per hectare in Canada is much lower compared to the US. Aquatic field studies conducted in Canada, including water monitoring studies, demonstrate glyphosate is detected less frequently and at lower concentrations than those reported in the US (Glozier et al. 2012, Hurley et al. 2012). The use of US field data for interpretation of the fate of glyphosate in Canada is challenging as the countries share only a few ecoregions, with climate and soil being different in much of the US where glyphosate is used as compared to Canada.

Terrestrial field dissipation studies

Laboratory studies conducted with glyphosate applied on different soils have DT_{50} (half-life) values ranging from 1 to 19.3 days, which classifies glyphosate as non-persistent to slightly persistent and indicates biotransformation by micro-organisms is effective.

Canadian terrestrial field dissipation studies show DT_{50} values ranging from 6 to 155 days for agricultural soils (average of less than 45 days) and from 24 to 82 days for forest soils (average of less than 55 days), similarly, in the US, DT_{50} values range from 1 to 174 days for agricultural soils (average of 41 days) and from <1 to 40.2 days for forest soils. The biotransformation of glyphosate is faster in forest ecosystems. In both environments, the compound is generally found in the upper soil horizons (0-15 cm depth) indicating overall that leaching to groundwater under field conditions is limited. The field data suggests glyphosate is non persistent to moderately persistent under field conditions and is not expected to carry over to the next year.

The wide range of dissipation rates, mainly in agricultural ecosystems, is likely a result of variation among soils, especially when considering foreign ecoregions (de Jonge et al. 2001; Vereecken, 2005, Borggaard and Gimsing, 2008, Farenhorst et al. 2009). Soil microbial activity may not always be efficient at transforming glyphosate or there may be other physical and chemical processes involved, reducing the rate of breakdown. Rapid adsorption to soil particles may play a role in preventing the transformation of glyphosate even in upper soil horizons where microbial activity is normally high and also when upper soil levels are not saturated with phosphate fertilizers (Helander et al. 2012). Preferential flow may play an important role, where root channels created by the death and decay of non-crop plants following glyphosate applications lead to the transport of glyphosate to lower soil horizons, however, leaching of glyphosate to deep soil horizons appears to be minimal.

Aquatic field dissipation studies

In general, aquatic field dissipation studies conducted in agricultural and forestry ecosystems in Canada and in the US indicate that glyphosate is non-persistent in natural waters (DT_{50} values ranging between ≤ 0.4 and 11.2 days).

Aquatic field dissipation studies conducted by Battaglin et al. (2014) and Battaglin and Koloc, (2014), show that glyphosate is readily transformed to AMPA by micro-organisms. Glyphosate was detected without AMPA in only 2.3% of samples, whereas AMPA was detected without glyphosate in 17.9% of samples. Both compounds were reported to be detected frequently in US soils and sediment, ditches and drains, precipitation, rivers, and streams, but less frequently in lakes, ponds, wetlands, soil water and groundwater. The study authors indicated that all concentrations of glyphosate measured were below the levels of concern for human and wildlife safety.

2.1.3 Runoff and aerial transport of glyphosate

Comment

Comments noted that the results of a runoff event studied in Argentina (Peruzzo et al. 2008) raise concerns about levels of glyphosate transported by runoff to aquatic environments. Glyphosate has been found in air and rain as demonstrated in a study conducted in Mississippi, USA (Chang et al. 2011, PMRA 2459642).

PMRA Response

The study of Peruzzo et al. 2008 suggests that rain events play an important role in transporting glyphosate present in the soil to stream water through runoff. In general, in the absence of mitigation measures to limit the run-off, especially when the ground is bare early in the season, this is not disputed. However, among all pesticides used in crop production in Argentina and elsewhere in the world, including Canada, glyphosate is among those that bind most strongly to soil. Despite glyphosate's high affinity for adsorption to soil particles, many studies have shown that the compound can find its way into water bodies, including studies from Italy (Screpanti et al., 2005; PMRA 2460734, Capri and Vicari, 2010; PMRA 2460735), the United States (Battaglin et al. 2005, PMRA 2423832, Scribner et al. 2007; PMRA 2460747, Newton et al. 1984; PMRA 1155371, Edwards et al. 1980; PMRA 2462226), Europe (Coupe et al. 2011; PMRA 2460748, Gregoire et al. 2010; PMRA 2462223, Siimes et al. 2006; PMRA 2462224), South America (Aparicio et al. 2013; PMRA 2462258) and Canada (Roy et al. 1989; PMRA 2460737, Struger et al. 2008; PMRA 1739313).

Many of the studies reported in the literature, including the one of Peruzzo et al. 2008, were conducted in ecoregions that are not equivalent to any Canadian ecoregions, meaning the soil and climatic conditions in study locations may not be relevant to conditions in Canada.

The amount of glyphosate applied in agricultural and forestry systems has increased since its first registration (about 40 years ago) and this is a factor in its frequent detection in surface waters and, more recently, in groundwaters of other countries outside North America (Sanchis et al. 2011, PMRA 2460750).

Examination of the factors controlling the transport of glyphosate to surface waters on a watershed scale is needed to determine which factors are important in this process and how these factors may change in importance, both spatially and temporally (Coupe et al. 2011, PMRA 2460748). The strong sorption of glyphosate to soil indicates that it expected to be poorly mobile. Recent studies on surface waters, both in Europe and in the Americas (North and South), suggest glyphosate could be transported to surface waters sorbed on soil particles. Detection in water may not only be a result of runoff, with drift, soil erosion, precipitation, and other processes having a role. In addition, the saturation of soils with phosphorus may play a role in reducing the sorption of glyphosate to soil particles, potentially increasing the amount carried in runoff.

Over the last two decades, Canadian growers have adopted best management practices on their farms (such as hedgerow, riparian strip, grass farm road, implementation of no till techniques leaving more plant biomass on the ground for runoff interception as well as the use of buffer zones) to avoid soil, fertilizer and pesticide losses from fields.

Runoff events can be difficult to predict and the presence of glyphosate in water as a result of runoff or spray drift is expected. Proper application timing and runoff/spray drift mitigation measures can reduce potential impacts.

Monitoring studies conducted throughout Canada indicate that glyphosate is rarely detected in groundwater. Although glyphosate is often detected in surface water, the concentrations detected are at relatively low levels that do not pose a risk of concern.

Glyphosate in the atmosphere

Available information indicates that limited amounts of glyphosate may enter the atmosphere at the time of spray application.

Glyphosate was not reported (among 49 compounds) in air or rain along the Mississippi river valley following an air survey campaign in 1995 (Foreman et al. 2000 and Majewski et al. 2000) but was recently reported to be frequently detected in air particles and rain from three agricultural areas of the Midwestern USA (Mississippi, Iowa and Indiana) with detection frequency ranging from 60 to 100% in air and rain in 2007 (Chang et al. 2011, PMRA 2459642 and Majewski et al. 2014). Glyphosate occurred at concentrations equal to or greater than the concentrations of other high-use herbicides previously studied in the Midwest (Waite et al. 2005). Unlike many other pesticides, the presence of glyphosate in air is reported to be due either to spray drift or wind erosion, because it is not volatile according to its low vapour pressure (1.3×10^{-7} Pa), Henry's law constant (2.1×10^{-9} Pa m^3/mole or 2.07 x 1014 atm. m^3/mole) and ionic character in moist soils (binding effect). Glyphosate was not measured or detected in the Canadian atmosphere during the Canadian Pesticide Air Sampling Campaign of 2003 (Yao et al. 2006).

In most studies, the maximum concentrations of glyphosate in air and rain correspond to the period of application and ranged from <0.01 to 9.1 ng/m^3 and from <0.1 to 2.5mg/L in air and rain samples, respectively. However, during a 2007 air survey by Majewski et al. (2000 and 2014) detectable concentrations of glyphosate were collected over the entire growing season, not just in spring as in previous years (before GMO's introduction around 1995), which is reported to be consistent with how glyphosate is now used on genetically modified crops for post-emergent weed control during the growing season. According to Chang et al. (2011), it is not known what percentage of the applied glyphosate was introduced into the air in 2007, but it is estimated that an average of 97% of the glyphosate in the air is removed by a weekly rainfall ≥30 mm. Based on the physical chemistry of glyphosate and the fact that the scale of use is lower in Canada as compared with the US, especially in the corn belt, the concentration of glyphosate in air is not expected to be of concern in Canada.

2.2 Ecotoxicological reviews

2.2.1 Beneficial insects impacted by the use of glyphosate

Comment

Comments noted that glyphosate negatively affects pollinator species (especially bees) and beneficial insect populations. GMO crops resistant to glyphosate, such as rapeseed crops or other GMO crops that include an insecticidal protein (for example, Bt) may have significant concentrations of these compounds in their flower pollen and nectar during the growing season following several applications of the herbicide. Bees foraging on these flowers may then transfer the glyphosate (with or without the insecticidal protein) through contaminated nectar and pollen when they feed young bees, which may have negative impact.

PMRA Response

The re-evaluation of glyphosate included a detailed analysis of studies to determine risks glyphosate may pose to pollinators and beneficial insects.

Acute oral and acute contact exposure of honey bees, and honey bee brood to technical glyphosate and glyphosate formulations obtained from the registrant did not result in mortality in laboratory studies. All acute oral and acute contact LD_{50} values were greater than the highest concentrations tested. The results of the studies indicate that glyphosate formulations and technical glyphosate are relatively non-toxic to bees. The use of glyphosate is expected to pose a negligible acute contact and oral risk to bees.

Direct exposure of bees to glyphosate through oral and contact tests represents a conservative exposure scenario as compared to the exposure bees receive from foraging on flowering rapeseed during a very specific time during the growing season.

A honey bee brood field study (Thompson, 2012) was reviewed by EFSA, 2015. Study results were also published in 2014 (Thompson et al. 2014), where the potential for glyphosate toxicity to developing honey bee larvae and pupae (tested with the Technical IPA salt and a glyphosate formulation (MON 52276)) when fed directly to honey bee colonies, showed a NOAEL (No Observed Adverse Effect Level) for brood development of honey bee colonies of 301 mg glyphosate a.e./L sucrose solution, the highest dose tested. EFSA concluded that glyphosate formulations (with POEA and without POEA) are relatively non-toxic to bees in terms of acute contact and acute oral routes to bees and honey bee brood.

Study results of Jadhav et al. 2008 showed no direct detrimental effects of glyphosate formulation with POEA on two water hyacinth biocontrol agents, *Neochetina eichhorniae* and *N. bruchi*. Jackson and Pitre (2004) demonstrated that the Roundup Ready soybean system, including applications of glyphosate, had no detrimental effects on pest and beneficial insects (*Cerotoma trifurcate* (Forster), *Spissistilus festinus* (Say), *Hypena scabra* (F.), and *Anticarsia gemmatalis* (Hübner) in wide-row soybean plantings. Study results of Hendrix and Parmelee (1985) showed that decomposition and microarthropod densities in glyphosate-treated grass litter (*Sorghum halepense*) were higher than untreated controls. Haughton et al. (2001a and 2001b) demonstrated that glyphosate spray applications were non-toxic to non-target spiders *Lepthyphantes tenuis* but that the loss of habitat was responsible for the reduction in abundance of the species. Similar observations and conclusions were found in tests carried out on the spider *Gonatium rubens* by Haughton et al. (1999).

Results of acute and chronic laboratory studies examining the toxicity of glyphosate formulations to the springtail *Folsomia candida* indicated that glyphosate formulations were not toxic to adult springtails up to the highest concentrations tested (Santos et al. 2012, PMRA 2469288). Results of acute and chronic laboratory studies examining the toxicity of glyphosate formulations to various other beneficial terrestrial arthropods on glass plates, leaf substrate and on artificial soil substrate generally indicate that glyphosate formulations were not toxic to the predatory mite (*Euseius victoriensis*) (Bernard et al. 2010; PMRA 2462245), the lacewing (*Chrysoperla carnea*) (SERA, 2010; PMRA 2469282), the hoverfly (*Episyrphus balteatus*) (Kedwards and Travis, 2001; PMRA 1213236), the carabid beetle (*Poecilus cupreus*) (Walker et al. 2000; PMRA 1213231) or the Staphylinid beetle (*Aleochara bilineata*) (Hermann, 2001; PMRA 1213232) up to the highest concentrations tested. Based on the weight of evidence, the risk to beneficial arthropods from the use of glyphosate is not expected to be of concern.

A study conducted by Murray et al. (2009) show that 50% of all wild bee species nest in a burrow in the ground. The intensification of agriculture may be contributing to the loss of foraging habitats and nesting sites for wild bees.

Studies by Duan et al. (2008) and Malone and Burgess (2009) show no adverse effects of glyphosate resistant Bt crops on exposed bees. These results are corroborated by Morandin and Winston (2003), Malone et al. (2007) and Babendreier et al. (2008), who looked at bumblebee colony exposure to Bt.

2.2.2 The Monarch Butterfly

Comment
Comments noted that the Monarch Butterfly is at risk due to the destruction of milkweed habitat resulting from the use of glyphosate.

PMRA Response
Monarch butterflies (*Danaus plexippus*) rely completely on plants in the milkweed family, especially the common milkweed (*Asclepias syriaca*) for both reproduction and larval food. Until recently, this plant was readily found in the Midwestern Corn Belt of the US and southern latitudes of Canada.

Monarch habitat has been documented to be in decline for the last 20 years in North America (Pleasants and Oberhauser, 2012, Brower et al. 2012, Bhowmik, 1994). Before the introduction of GMO crops, glyphosate was applied in spring at the pre-emergence stage of crops and had limited impact on the survival of the common milkweed (Waldecker and Wyse, 1985, Doll 1998). But recent introduction of GMO crops resistant to glyphosate enables herbicide treatments to be done very late in the growing season (Carpenter and Gianessi, 1999 and Duke and Powles, 2008), impacting the last emerged shoots of the common milkweed, and thus, compromising its survival.

For the monarch, the decline in milkweed represents a threat since the plant is now incapable of re-colonizing fields after GMO crop harvest, especially in the corn belt of the USA and now in the low latitude fields of Canada. The discussion is open as to what the grower should do regarding the competition of the milkweed and other weeds against his own crop within a specific field and/or the protection of the milkweed within the same field.

In fact, glyphosate is not meant to destroy monarch habitats outside of field limits. This is why buffer strips along agricultural fields close to hedgerows and other terrestrial and aquatic habitats exist, and why buffer zones are required to mitigate the impact of drift on non-target organisms located in aquatic and terrestrial habitats. In addition to agricultural pressures, Monarch habitat is also threatened by natural disasters (fire, drought, flood, etc.) and urbanization.

Canada is working with the US and Mexico to coordinate Monarch conservation efforts and is a member of the Trinational Monarch Science Partnership; the government of Canada's participation is led by Environment and Climate Change Canada. Domestically, the federal government has posted its proposed management plan for Monarch on the Species at Risk Public Registry, is funding research on Monarch habitat, and is using its Species at Risk funding programs to support Monarch and pollinator conservation.

2.2.3 Effect of glyphosate and its different formulations on soil microbes

Comment
Comments noted that PRVD 2015-01 did not address serious concerns related to glyphosate's chelation activity and antimicrobial (and antibiotic) properties. Recent published articles have reported that glyphosate and genetically modified (GM) crops can impact soil microbial populations (Fernandez et al. 2009). Glyphosate, like an antibiotic, may kill fungi in the soil, preventing soil microbes from delivering nutrients (minerals in particular) to plants and may increase plant diseases. Glyphosate may act on the shikimate pathway of gut bacteria. Research methods used in studies are not sensitive enough to properly determine the impact glyphosate has on soil microbial populations.

PMRA Response
Although the PMRA is aware that interactions between soil bacteria, fungi and plant root systems can improve plant health, the PMRA does not assess risks to soil microorganisms. Negative impacts have been observed on specific soil microbe strains, but overall, evidence suggests glyphosate end-use products have a low impact on deleterious and beneficial soil microbes following application. Glyphosate contributes to sustainable agricultural systems by reducing the need for cultivation (for example, no-till technique), increasing plant biomass on the ground, increasing the soil organic matter content, improving soil structure and reducing soil erosion and run-off. The fact that glyphosate use has been increasing since its first registration in Canada in 1976 demonstrates that growers have adopted the use of glyphosate and in turn the use of glyphosate-resistant crops very rapidly. If glyphosate had a meaningful negative impact on soil microbial activity over this 40 year use history, growers would not have been so quick to adopt and continue to use the product. The effects on soil microflora would have the strongest impact on crops grown on the fields. Areas away from the site of application are not likely to be negatively impacted.

2.2.4 Birds and mammals exposed to glyphosate and its formulations containing polyethoxylated tallow amine (POEA)

Comment
Comments noted that glyphosate has negative effects on non-target animals. Studies from the United Kingdom demonstrate that glyphosate contributes to a decline in bird species and is also believed to be responsible for increased livestock diseases, such as infertility, nutrient deficiencies (connected to Mn deficiencies), stillbirths, birth defects and abnormal bone formation. Glyphosate, in combination with surfactants used in glyphosate end use products (for example, POEA), is also more toxic to non-target organisms (animals and plants) than glyphosate alone.

PMRA Response
Birds
As presented in the PRVD2015-01, several oral, dietary and chronic toxicity studies were conducted with glyphosate technical and formulations on the bobwhite quail, *Colinus virginianus*, and the mallard duck, *Anas platyrhynchos*. Toxicity studies were also available for the canary, *Serinus canaria* (acute oral exposure with technical glyphosate) and the chicken (21-day dietary exposure with a glyphosate formulation). Glyphosate technical was not toxic to birds

on an acute oral, dietary or reproductive basis up to the highest concentrations or doses tested (PRVD2015-01). Similarly, glyphosate formulations are not particularly toxic to birds on an acute oral and dietary basis (reproduction tests were not available with glyphosate formulations). While acute oral exposure to glyphosate formulations resulted in bird mortality at high doses, glyphosate formulations were not toxic to birds up to the highest concentrations tested when exposure occurred through the diet. There is no indication that glyphosate formulations containing the surfactant POEA are more toxic to birds than formulations without it. Endpoints and risk quotients calculated using these studies are conservative as none of the toxicity studies conducted with technical glyphosate resulted in measured toxic effects in birds.

Although bird toxicity studies indicate that acute oral exposure to high doses of wet, unaltered, glyphosate formulations can result in effects, these effects are not observed when exposure occurs from dried residues of the formulation in the diet. Exposure to glyphosate formulations through the consumption of contaminated food items is a more relevant route of exposure for the environmental assessment than acute oral exposure to the wet formulation. The time period during which wet unaltered formulated product would be present on food items is very limited. Exposure is likely to be mostly from ingestion of dried residues on food items. It is noted that exposure via preening, which may be a relevant exposure route for wet formulation, is not considered in the current assessments. Thus, more weight is given to conclusions of the dietary assessment than to the acute oral assessment. The risk to birds from acute oral, dietary and reproduction exposure to glyphosate and its formulations is expected to be low.

One comment also reported the study of Newton (2004) as evidence of major farmland bird declines in the UK in connection with herbicide uses (not specifically glyphosate) and agricultural practices that would be responsible for the reduction of habitat and/or food available to many species.

Other studies indicate minimal impacts or even the absence of negative impacts on bird community structure and densities following glyphosate treatments in forests and vegetative changes after clearcuts (Morrison and Meslow, 1984; Mackinnon and Freedman, 1993). Other studies (Linz et al. 1992, Linz et al. 1994, Linz et al.1995, Linz et al. 1996a, Linz et al. 1996b, and Solberg and Higgins, 1993) show that glyphosate treatment in wetlands to control invasive species such as cattails (*Typha* spp.) was efficient and had positive impacts by restoring bird habitats (open water) and by increasing original population and diversity.

A review by Sullivan and Sullivan (2003; PMRA 2469318) reported that species richness and diversity of songbirds and small mammals were little affected by glyphosate-induced habitat alteration. Some species declined rapidly following treatment, whereas others increased in abundance. The effect of glyphosate on large mammalian herbivores was measured by the abundance of animals and food plants and by habitat use. Hares and deer were little affected, whereas reductions in plant biomass and related moose forage and habitat use generally occurred for the first few years after treatment, but not thereafter.

Studies in North America have identified habitat loss as the major cause of bird declines over the last 25 years (Santillo et al. 1989 and Hardy and Desgranges, 1990).

Mammals

Numerous acute oral toxicity studies on mammals were available for glyphosate technical and various glyphosate formulations. There is no indication that formulations containing the surfactant POEA are more toxic to mammals than formulations without POEA. Six multi-generation reproduction studies with exposure through the diet were available for technical glyphosate. No reproduction studies with glyphosate formulations were available.

Most mammalian toxicity studies show that exposure to high levels of glyphosate technical or its formulations does not result in toxic effects on mammals. Based on 60 acute oral studies, toxic effects were observed at high doses only in three studies conducted with glyphosate technical, and eight studies with glyphosate formulations. The majority of the available data indicate that risks to mammals following acute oral exposure to glyphosate and its formulations are low. Acute risks to mammals would be restricted to on-field exposure of only a few guilds (herbivores and insectivores). No reproductive risks to mammals are expected from the use of glyphosate. In addition, there are no incident reports for mammals related to the use of glyphosate.

2.2.5 Risk to Amphibians

Comment

Comments noted that glyphosate contributes to the decline of frog abundance. Glyphosate alone (Paganelli et al. 2010), and in combination with POEA, poses risks to amphibians according to studies of Relyea (2005a, 2005b and 2005c) and review of Annett et al. 2014.

PMRA Response

Toxicity data were available for 32 species of amphibians at various stages of development. As is shown with invertebrates and fish, the toxicity of technical glyphosate and its salts and glyphosate formulations containing non-POEA surfactants to amphibians is relatively low (acute LC_{50} = >17.9–7297 mg a.e./L) compared with glyphosate formulations containing POEA (acute LC_{50} = 0.8–51.8 mg a.e./L). Similarly, the results from subchronic and chronic laboratory studies and outdoor mesocosm studies with amphibians demonstrate that exposure to glyphosate formulations containing POEA elicit lethal and sublethal effects (for example, reduced body size, abnormal development, decreased time to metamorphosis) at relatively low concentrations (LC_{50} = 1.0–22.8 mg a.e./L, NOEC = 0.006 - >1.8 mg a.e./L).

Although acute studies showed no negative impacts on amphibians from glyphosate TGAI and formulations that do not contain POEA, a refined risk assessment conducted on amphibians (including frogs) exposed to glyphosate formulations containing POEA (lab tests) indicated that the level of concern was slightly exceeded (RQ = 1.1-1.2) for end-use products containing the surfactant POEA and tested in lab. Level of concern was not exceeded for refined mesocosm studies. Relyea (2005a and b) demonstrated a glyphosate formulation containing the surfactant POEA was responsible for the kill of 68-86% of juvenile amphibians exposed. This study, along with other amphibian studies, was considered in the re-evaluation of glyphosate and used to determine an HC_5 endpoint value from an SSD analysis. Results revealed an acute and chronic HC_5 of 0.93 and 0.86 mg a.e./L, respectively for glyphosate formulations containing the POEA surfactant that were used in the refined risk assessment. As a result, mitigation measures, in the form of no spray buffer zones, are identified on product labels and are required to protect amphibians. Risks to amphibians are not of concern if labelled spray buffer zone requirements are followed.

Annett et al. (2014), in their review, report the mode of action of different glyphosate formulations and their potential negative impact related to the inhibition of the enzyme acetylcholisesterase of some aquatic species as well as the oxidative stress due to Reactive Oxygen Species (ROS) causing damage to nucleic acid, lipids and proteins in aquatic species such as amphibian and fish that can lead to cell death. Studies reviewed, and reported by Annett et al. (2014) were also reviewed by the PMRA, with many of the reported endpoints being used by the PMRA in the risk assessment of glyphosate.

While there is evidence from laboratory studies suggesting that glyphosate products containing POEA are more toxic to amphibians than glyphosate alone, when considered in the context of all the studies available, particularly field studies conducted under actual use conditions, there is no compelling or credible evidence that gives rise to a serious possibility that glyphosate products containing POEA may cause an unacceptable environmental risk. In addition, while lower tier studies conducted in a laboratory showed potential for effects, a field study conducted under operational conditions (Thompson et al. 2004, PMRA 2032071) showed no significant adverse effects on amphibians. Moreover, glyphosate products containing POEA are used in forestry to prepare the site for reforestation which requires that the products be applied only once per silviculture cycle; typically equating to once every 50 to 80 years. As such, the potential for amphibian exposure to glyphosate products is limited in silviculture. Based on these findings, the PMRA concluded that there were no reasonable grounds to believe that the environmental risk to amphibians in small ephemeral forest wetlands from the spraying of glyphosate products was unacceptable.

2.2.6 Other Aquatic organisms

Comment

Comments noted that the following studies were not taken into account in the re-evaluation of glyphosate: Vera et al. 2010 (periphyton), Fairchild et al. 2002 (Atlantic salmon), and Sihtmae et al. 2013 (aquatic invertebrates).

PMRA Response

Periphyton

The study of Vera et al. 2010 entitled ''New evidence of Roundup impact on the aquatic periphyton community and the quality of freshwater ecosystems'' (Ecotoxicology 19:710-721) was in fact considered qualitatively in the re-evaluation, but no endpoints were available in the study to be used as part of the SSD analysis. The study of Bonnineau et al. 2012 (PMRA# 2462244) on periphyton was preferred and the freshwater algae acute 6hr-EC_{50} endpoint of 8.7 mg a.e./L was used in the re-evaluation of glyphosate and presented in PRVD2015-01.

Atlantic salmon

The study of Fairchild et al. 2002, entitled "Effects of freshwater contaminants on marine survival in Atlantic salmon" (NPAFC Tech Report No. 4) was examined and it was determined that the study is related to the active atrazine and does not report on glyphosate.

Aquatic invertebrates
The study of Sihtmae et al. 2013 entitled "Ecotoxicological effects of different glyphosate formulations" (Applied Soil Ecology 72:215-224) was indeed used in the re-evaluation of glyphopsate. The freshwater invertebrate endpoint values reported by Sihtmae et al. 2013 (PMRA 2574468) were used in the determination of HC_5 values from a SSD analysis. Refer to response 2.3.2 below.

2.2.7 Endocrine disruption

Comment
Comments noted that the PMRA should phase out the use of products containing glyphosate based on articles that have identified glyphosate as an endocrine disruptor.

PMRA Response
The USEPA's Endocrine Disruptor Screening Program (EDSP) is currently working to validate the assays proposed by the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), many of which are being validated in coordination with the OECD through the Endocrine Disrupters Testing and Assessment (EDTA) and the Validation Management Groups (VMGs). The results of screening tests for glyphosate are available on the following website: (http://www2.epa.gov/sites/production/files/2015-06/documents/glyphosate-417300_2015-06-29_txr0057175.pdf).

Although the study by Antoniou et al. 2012 raised concerns regarding the potential impact of glyphosate as an endocrine disruptor, the conclusion is that glyphosate demonstrates no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways in mammals or wildlife. Based on weight of evidence considerations, mammalian or wildlife EDSP Tier 2 testing is not recommended for glyphosate. Also refer to response to comment 1.1.12.

2.2.8 Bioaccumulation

Comment
Comments questioned if glyphosate can accumulate in the body over time and how levels of glyphosate are monitored to ensure that it does not go above acceptable limits that could cause detrimental health effects to animals?

PMRA Response
Information available on the bioaccumulation potential of glyphosate is presented in the PRVD 2015-01. Glyphosate is not expected to bioaccumulate due to its high polarity (log K_{ow} = -2.8 to -0.67) and anionic character (Mensink and Janseen, 1994, PMRA 2462253 and Villeneuve, J., 2012 (PMRA 2203372)). A maximum bioconcentration factor (BCF) of 1.6 was reported for bluegill sunfish exposed to 0.6 mg/L for 28 days (Wang et al. 1994b; PMRA 2460743 and Takacs et al. 2002; PMRA 2462252). BCF values of 12 to 35.4 and 10 to 42.3 for tilapia and carp, respectively were also reported by Wang et al. 1994b (PMRA 2460743). Channel catfish, largemouth bass and rainbow trout exposed to 10 mg/L glyphosate for 14 d had BAFs of 0.18, 0.04, and 0.03, respectively (Kramer and Beasley, 1975, PMRA 1182548).

2.2.9 Science based approach and the use of independent scientific studies in the environmental risk assessment.

Comment
Various stakeholder organizations emphasized the importance of a science-based approach and agreed with the proposed regulatory label changes. Other commenters encouraged to use a number of different sources of information that claim glyphosate poses an environmental risk. Sources of information from various non-governmental organizations or independent researchers were provided. In addition to registrant submitted studies, work done by third parties (independent research) should be used in assessing the environmental effects of glyphosate and in making the final re-evaluation decision.

Some commenters believe that the environmental risk assessment for glyphosate was conducted using only studies provided by the registrants and that there has not been enough long-term testing of glyphosate done by independent scientists. Reviewing studies conducted and provided by the company that is seeking registration of the product is perceived as a conflict of interest and highly biased as these studies are not peer reviewed by the scientific community. Reference was provided to a number of published scientific studies that link glyphosate to environmental and agronomic effects.

PMRA Response
The environmental risk assessment of glyphosate was conducted using a science-based approach and included consideration of a large volume of literature. In addition to registrant supplied data, more than 1500 scientific articles related to glyphosate were examined, with approximately 250 of these studies being deemed relevant and useful for consideration in the environmental risk assessment. Values obtained from the public literature were used in combination with the registrant data set in order to strengthen the environmental risk assessment. Due to the tremendous amount of endpoint data available for different aquatic and terrestrial organisms, SSD analysis was employed to determine HC_5 and HD_5 values that were used in the risk assessment. Also refer to response to comment 1.1.14.

2.2.10 Assessment of formulations

Comment
Commenters questioned why the formulations of glyphosate products are not assessed for their environmental effects. Environmental effects discussed in the PRVD2015-01 were based primarily on the active substance (in other words, glyphosate).

PMRA Response
PRVD2015-01 includes risk assessments for not only the technical active ingredient, but also the various formulations, including those that contain POEA. Endpoints using values from EUPs were used to derive HD_5/HC_5 values from SSD calculations when possible. The risk assessment includes a comparison of the exposure of terrestrial and aquatic organisms to technical glyphosate and the formulations.

2.3 Risk assessment and methodology

2.3.1 Endpoint selection

Comment
Some endpoints used in the terrestrial and aquatic plant risk assessment as well as the risk assessment for aquatic organisms were inappropriate. The quality of some of the data used in the risk assessment was not clear and was questionable. Specific studies that were at issue were identified for the PMRA to reconsider. The process used to review and ensure the quality of open literature studies used in the risk assessment needs to be more transparent.

PMRA Response
Endpoints derived from unpublished registrant/applicant submitted data follow guidelines set by regulatory bodies and are subject to good laboratory practice standards. These studies have clear objectives, scientific and analytical protocols, and the data has been subject to appropriate statistical analysis. On the other hand, published scientific papers are written in a concise way in order to bring enough information and details for the reader to accept or reject the conclusion of the author(s). Although published scientific articles are subject to a scientific peer review that strengthens their validity, information in published studies must have sufficient detail so that the scientific methods (protocol) and the results obtained are reproducable. Unfortunately, many published scientific studies lack sufficient detail, reducing confidence in the conclusion reached by the author(s). As a result, some published scientific papers are rejected when reviewed by the PMRA during the re-evaluation process. (Refer also to response to comment 1.1.14).

That said, as a result of comments received during the comment period for the PRVD2015-01, endpoints questioned in the comments have been re-examined and changes to the risk assessment have been made based on a revised assessment of their validity. References associated with endpoint values are presented in the tables found in (Appendix III).

2.3.2 SSD model

Comment
The methodology for deriving Species Sensitivity Distributions (SSDs) is not fully described in the PRVD and the requirements for inclusion of endpoints is not discussed. The use of a combination of terrestrial plant EC_{25} and EC_{50} endpoints for vegetative vigour in SSD calculations should be reconsidered.

PMRA Response
The toxicity data analysis includes the determination of HC_5 or HD_5 values using an SSD or species sensitivity distribution. An SSD is a plot of all species' toxicity endpoints within a taxonomic group against a cumulative density function. An SSD is determined by fitting a theoretical distribution to the data set, such as a log-normal distribution, and allows the derivation of community level threshold concentrations such as the HC_5. The hazardous concentration (HC_5) or dose (HD_5) to five percent of species is calculated for acute and chronic data sets separately, using the acute LC_{50}/EC_{50} values and chronic NOEC/NOEL values, respectively. An SSD is constructed for acute and chronic effects for every taxonomic group where sufficient toxicity data are available. Acute toxicity data generally refers to short term studies, with the endpoints (LC_X or EC_X) being derived from effects on survival or other

endpoints considered to affect survival. Chronic and sub-chronic studies generally aim to determine sublethal effects and the associated NOEC or NOEL concentration. Different endpoints can also be used in SSDs such as the EC_{25} for terrestrial plants or other EC_X value such as an $EC_5/_{10}$ may be considered relevant and appropriate to the assessment. If SSDs cannot be calculated, the most sensitive endpoints with an appropriate uncertainty factor are used in risk assessment.

The software program ETX 2.1 is used with the log-normal model to generate SSDs where sufficient toxicity endpoints are available for different taxonomic groups. The median HC_5 values are reported for SSDs. The variability in the data sets is indicated not only by the upper and lower bound HC_5 estimates but also the confidence limit of the fraction of species affected (FA), which indicates the theoretical minimum and maximum percent of species that could be affected based on the available data when the population is exposed to the HC_5 concentration.

SSDs were determined for glyphosate herbicide for the following taxonomic groups (results are reported in Appendix III Tables 1 to 3):

- Freshwater organisms: invertebrates, fish, algae, amphibians, aquatic plants
- Marine organisms: fish, invertebrates and algae
- Terrestrial organisms: plants (crop and non-crop)

Where an HC_5 value cannot be determined due to insufficient species data or lack of model fit, etc., the most sensitive species endpoint is reported in summary tables without the use of uncertainty factors. Where multiple data points are available for one species, a geometric mean value is used to represent the species' sensitivity. The treatment of toxicity data is such that it allows quantitative comparisons and predictions including consistency of exposure concentration units, ecological relevance and comparability of measurement endpoints, and types of test chemicals, or duration of exposure.

All data sets were grouped by test material type including technical grade active ingredient (TGAI, includes all forms of glyphosate actives), end-use products containing the surfactant POEA (EUP + POEA), end-use products which do not contain POEA (EUP NO POEA), POEA alone and the glyphosate transformation product AMPA. All toxicity values were normalised to acid equivalent (a.e.).

Results of SSD analysis:
Glyphosate shows equal toxicity to many aquatic taxonomic groups, both acutely and chronically. The most acutely sensitive aquatic taxonomic groups are freshwater plant (overspray on aquatic macrophyte; Er_{50} of 38 g a.e/ha), freshwater and marine invertebrates, and freshwater algae (HC_5 = 0.1mg a.e./L). The lowest chronic toxicity threshold values were determined for freshwater and marine fish (NOEC = 0.28 and 0.1 mg a.e./L, respectively) and freshwater plants (chronic EC_{50} = 0.11 mg a.e./L). The most sensitive terrestrial plant endpoint for crops and non-crops is the HD_5 of EC_{50} value of 0.0658 kg a.e./ha for EUPs that contain, or do not contain POEA, based on plant vegetative vigor endpoints.

As observed for amphibian in previous section 2.2.5, it is noted that the formulated products of glyphosate are generally more toxic to some organisms than the active ingredient, as in the case of freshwater invertebrates which are two orders of magnitude (100x) more sensitive to formulations containing POEA vs. the active ingredient. Freshwater fish and plants are also more sensitive to EUPs. Marine fish on the other hand are most sensitive, on an acute basis, to the parent chemical.

Therefore the SSD analysis results indicate that the most sensitive population level aquatic toxicity threshold value (HC_5) is 0.1 mg a.e./L, based on acute and chronic endpoints for several taxanomic groups including freshwater and marine invertebrates, aquatic plants (except overspray), algae and fish. While the most sensitive population level terrestrial toxicity threshold value (HD_5 of EC_{50}) is 0.0658 mg Kg a.e./ha, based on acute toxicity to plants (crops + non-crops exposed to glyphosate formulations containing POEA + glyphosate formulations without POEA).

2.3.3 Buffer zone calculations

Comment
Comments noted that the buffer zone sizes should be recalculated based on reconsideration of acceptability of endpoints. Buffer zone sizes should be set based on scientific evidence and valid endpoints and no increase should be implemented if no such evidence exists. Please explain why buffer zones are different for treated areas of more than 500 ha and those that are less than 500 ha.

PMRA Response
The PMRA agrees with the fact that buffer zone sizes should be set based on scientific evidence and valid endpoints and no increase or decrease should be implemented if no such evidence exists. The methodology used by the PMRA to calculated buffer zones is based on scientific evidence and valid endpoints.

Endpoints were reconsidered following identification of questionable studies, which lead to changes in the endpoints included in the SSDs and the determination of HC_5 values, especially for aquatic organisms. Buffer zones have been recalculated as a result of the changes in the SSD calculations.

The reason why buffer zones are different for treated areas of more than 500 ha and those that are less than 500 ha. is the following:

The AGDISP software model (version 8.21) used by the PMRA to calculate aerial buffer zones takes into account the cumulative downwind drift associated with the number of flightlines made over a treated surface area with an aircraft. A forest surface area of more than 500 ha is considered as 'woodland' and is modelled using 50 flightlines as a realistic scenario. A forest surface area of less than 500 ha is considered as 'woodlot' and requires only 10 flightlines. As such, cumulative drift may be more significant in woodlands than in woodlots and consequently buffer zones may be larger in woodlands than in woodlots. Updated buffer zone tables are reported in Appendix IV, Tables 1 and 2.

2.4 Aerial spraying of forests

Comment
One Aboriginal group commented that aerial spraying of forests with glyphosate impacts the environment.

PMRA Response
As noted in response to comment 2.2.5, glyphosate is used for forest site preparation and plant release (conifers and deciduous trees) after trees are harvest. This use is expected to occur once every 50-80 years. As such, glyphosate exposure to forest is extremely low. In addition, glyphosate does not persist in the terrestrial environment, with DT50s ranging from 24 to 82 days in forest soils (average of less than 55 days).

For the protection of aquatic habitats, no spray buffer zones of 1 to 10 meters are required when glyphosate formulations that contain POEA are applied for forest site preparation and plant release by air. A buffer zone is defined as the distance between the point of direct pesticide application and the nearest downwind boundary of a sensitive habitat. Glyphosate does not persist in water (DT50s range from 0.4–11.2 days).

3.0 Comments Related to the Value Considerations

3.1 Glyphosate has value in contributing to Canadian agriculture and non-agricultural land management

Summary of Comments

- glyphosate is an important and cost effective weed management tool in crop production in that it can be applied at varying points of the cropping cycle from preplant to post-harvest.
- the application of glyphosate prior to harvest is important in terms of advancing the maturity and/or uniformly desiccating the crop and to control late season weeds that can interfere with harvesting operations and reduce crop quality.
- glyphosate with its unique mode of action remains an important tool for broad spectrum weed control, including of perennial, invasive and noxious weeds
- it allows the Canadian agricultural sector to remain competitive with those of its trading partners
- it remains an important tool for advancing conservation tillage, such as no-tillage and reduced tillage systems, that reduce soil erosion and increase soil organic matter
- it is used to control invasive plants to foster biodiversity by allowing native plant communities including those containing endangered or rare species, to be preserved or re-established.

PMRA Response
As stated in the PRVD2015-01, the PMRA acknowledges that glyphosate plays an important role in weed management in both Canadian agriculture and non-agricultural land management

3.2 Glyphosate has no value considering the risks to the environment and human health.

PMRA Response
The value of glyphosate to Canadian agriculture and non-agricultural land management is a result of this product's unique mode of action, diverse use pattern, and broad spectrum of weed control. As indicated in PRVD2015-01, based on a review of the science, the PMRA has concluded that this product is unlikely to affect human health or pose an unacceptable risk to the environment when used in accordance with label directions.

4.0 Other Comments Related to the Use of Glyphosate

4.1 Weed resistance

Comment
Comments noted that repeated use of glyphosate and heavy reliance on glyphosate to control weeds in today's agriculture practices increase weed resistance. PMRA has not addressed the issue of weed resistance in its re-evaluation of glyphosate. There is no mention of glyphosate-resistant weeds anywhere in the Environmental Considerations of the PMRA's Proposed Re-evaluation decision for glyphosate. A report recently published by the Canadian Biotechnology Action Network (CBAN) reveals that "there are five species of glyphosate-resistant weeds now found in Canada". An online survey of farmers from 2013 estimated that more than one million acres of Canadian farmland had glyphosate resistant weeds.

PMRA Response
The PMRA is aware of the fact that the current agricultural production system relies heavily on glyphosate, resulting in more and more occurrences of glyphosate-resistant weeds. Kochia, Canada fleabane, giant ragweed and common ragweed are examples of such resistant weeds reported in Canada. These glyphosate-resistant weeds are increasingly becoming challenge to the agricultural production system. In order to prevent or delay the development of glyphosate-resistant weeds, it is crucial to maintain diversity in weed management practices. From the regulatory perspective, the PMRA developed the resistance-management labelling program in 1999 with an aim to mitigate the risks for resistance development. Participation in this program is on a voluntary basis, but registrants are encouraged to add the resistance-management grouping symbols and resistance management statements to both new and existing product labels (Regulatory Directive DIR2013-04, *Pesticide Resistance Management Labelling Based on Target Site/Mode of Action)*. To date, the majority (about 95%) of labels for products containing glyphosate comply with the resistance-management labelling. Other organizations are more closely involved with improvements to agricultural practices.

4.2 Invasive species

Comment
Comments noted that herbicide treatments such as glyphosate are needed to control invasive species in standing water, such as *Phragmites australis* (2015 Resolution of the Canadian Federation of Agriculture Annual General Meeting).

PMRA Response
Before a pesticide is approved for use in Canada, it must undergo a thorough pre-market science-based risk assessment and meet strict health and environmental standards, and the product must have value. The use of glyphosate to control invasive species in standing water was not registered in Canada, and therefore was not considered during the re-evaluation.

The PMRA is aware of the rise of *Phragmites* in Canadian wetlands, and has been working with provincial partners to find solutions such as emergency registration where needed. An emergency use will be considered only if the product is efficacious and risks deemed acceptable.

4.3 Treaty rights and the duty to consult First Nations

Comment

One Aboriginal group commented that aerial spraying on traditional lands is a violation of treaty rights and it is a constitutional obligation for Health Canada to consult. The PMRA is obligated to hear oral testimony in their territory as a form of evidence.

PMRA Response

Concerns expressed by the aboriginal group in their written submission and in subsequent conversations, were identified as being related more to forest management practices and not specific to the use of this particular herbicide.

Following harvest, Canadian forests are either allowed to regenerate naturally or are re-planted with a crop tree species as part of a forest management plan. Glyphosate, or other herbicides, can be applied in a managed forest to control naturally occurring vegetation that could out compete newly planted crop tree seedling (for example, pine or spruce trees) for nutrients, light and space. Herbicides are also used in clearing logging roads and rights of way. As with other land management uses of pesticides such as agriculture, the use of herbicides in forestry operations can reduce biodiversity (for example, loss of grasses, raspberry and non-crop tree species, such as birch or aspen) in the application areas for a period of time.

Except on federal lands, the management of natural resources, such as forests, is the responsibility of provincial governments. Provincial ministries of natural resources are better informed about the local conditions and are generally responsible for approving sustainable forest-management plans. These plans indicate which land will be allowed to regenerate naturally and which will be re-planted and managed (with or without herbicides). If a herbicide is to be used, it must a product that is authorized by Health Canada's Pest management Regulatory Agency for forestry application. It the product is to be applied by air, permits are required, generally from provincial ministries of the environment, prior to application. Consultations with the aboriginal community on herbicide use in forestry can be most effectively done by considering forest management plans and the local land use requirements. It is recommended that the group continue to raise their concerns with the appropriate provincial authorities

Other concerns that were raised by this group regarding the impact of glyphosate use on human health and the environment were addressed under responses 1.3.8 and 2.4.

Appendix II Registered Products Containing Glyphosate in Canada as of 16 September 2016

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	29219	GLYPHOGAN PLUS LIQUID HERBICIDE	GPI-356;	SN-SOLUTION	C+R
ALBAUGH LLC	28322	CLEAROUT 41 PLUS HERBICIDE SOLUTION	GPI-360;	SN-SOLUTION	C
	31913	GLYPHOSATE 480	GPI-480;	SN-SOLUTION	C
ALLIGARE, LLC	30093	ALLIGARE GLYPHOSATE 4+	GPI-360;	SN-SOLUTION	C
AGROMARKETING CO. INC.	30721	NASA 36	GPI-360;	SN-SOLUTION	C+R
AGRI STAR CANADA ULC.*	29995	CRUSHR PLUS	GPI-360;	SN-SOLUTION	C
	32181	CRUSHR 480	GPI-480;	SN-SOLUTION	C
	31655	AGRI STAR CRUSHR 540	GPP-540;	SN-SOLUTION	C
DOW AGROSCIENCES CANADA INC.	30958	ENLIST DUO HERBICIDE	GPX-204; DXJ-194;	SN-SOLUTION	C
	30960	GF-2726 TSOY HERBICIDE	GPX-204; DXJ-194;	SN-SOLUTION	C
	27394	PREPASS B HERBICIDE (A COMPONENT OF PREPASS HERBICIDE)	GPI-360;	SN-SOLUTION	C
	27615	VANTAGE PLUS MAX HERBICIDE SOLUTION	GPI-480;	SN-SOLUTION	C
	28245	MAVERICK II HERBICIDE SOLUTION	GPI-480;	SN-SOLUTION	C
	28540	ECLIPSE II B HERBICIDE	GPI-480;	SN-SOLUTION	C
	28977	MAVERICK III HERBICIDE	GPX-480;	SN-SOLUTION	C
	29033	ECLIPSE III B HERBICIDE	GPX-480;	SN-SOLUTION	C
	29652	PREPASS XC B HERBICIDE (A COMPONENT OF PREPASS XC HERBICIDE)	GPX-480;	SN-SOLUTION	C
	29994	VANTAGE XRT HERBICIDE	GPX-480;	SN-SOLUTION	C
	26171	VANTAGE PLUS HERBICIDE SOLUTION	GPI-360;	SN-SOLUTION	C+R
	26172	VANTAGE HERBICIDE SOLUTION	GPI-356;	SN-SOLUTION	C+R
	26884	VANTAGE FORESTRY HERBICIDE	GPI-356;	SN-SOLUTION	C+R
	29588	GF-772 HERBICIDE	GPI-360;	SN-SOLUTION	C+R
	29773	DEPOSE HERBICIDE SOLUTION	GPI-356;	SN-SOLUTION	C+R
	30516	VANTAGE MAX HERBICIDE	GPS-480;	SN-SOLUTION	C+R
	28840	VP480 HERBICIDE	GPX-480;	SN-SOLUTION	C+R
	29774	DURANGO HERBICIDE	GPX-480;	SN-SOLUTION	C+R
	30423	PREPASS 480	GPX-480;	SN-SOLUTION	C+R

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
		HERBICIDE			
	32314	GF-2018 HERBICIDE	GPX-480;	SN-SOLUTION	C+R
EZJECT, INC.	21262	DIAMONDBACK HERBICIDE SHELLS	GPI-0.15;	PA-PASTE	C
FMC CORPORATION	27287	GLYFOS AU SOLUBLE CONCENTRATE HERBICIDE	GPI-360;	SN-SOLUTION	C
	28925	CHEMINOVA GLYPHOSATE (TM) II	GPI-356;	SN-SOLUTION	C
	29363	GLYFOS BIO HERBICIDE	GPI-360;	SN-SOLUTION	C
	29364	GLYFOS BIO 450 HERBICIDE	GPI-450;	SN-SOLUTION	C
	30234	FORZA BIO SILVICULTURAL HERBICIDE	GPI-360;	SN-SOLUTION	C
	30235	FORZA BIO 450 SILVICULTURAL HERBICIDE	GPI-450;	SN-SOLUTION	C
	24359	GLYFOS SOLUBLE CONCENTRATE HERBICIDE	GPI-360;	SN-SOLUTION	C+R
	26401	FORZA SILVICULTURAL HERBICIDE	GPI-360;	SN-SOLUTION	C+R
	28924	GLYFOS SOLUBLE CONCENTRATE HERBICIDE II	GPI-360;	SN-SOLUTION	C+R
INTERPROVINCIAL COOPERATIVE LIMITED	26846	GLYPHOSATE HERBICIDE - AGRICULTURAL & INDUSTRIAL	GPI-360;	SN-SOLUTION	C
	29216	GLYPHOSATE WATER SOLUBLE HERBICIDE	GPI-309(+51);	SN-SOLUTION	C
	27988	IPCO FACTOR 540 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	31199	FORTRAN 540 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	31598	CO-OP VECTOR 540 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	29775	MATRIX HERBICIDE SOLUTION	GPX-480;	SN-SOLUTION	C+R
	30319	VECTOR HERBICIDE SOLUTION	GPX-480;	SN-SOLUTION	C+R
	31090	RIVET HERBICIDE	GPX-480;	SN-SOLUTION	C+R
JOINT GLYPHOSATE TASK FORCE, LLC	30678	JGTF GLYPHOSATE HERBICIDE	GPI-360;	SN-SOLUTION	C+R
LOVELAND PRODUCTS CANADA INC.	30076	MAD DOG PLUS	GPI-360;	SN-SOLUTION	C+R
MEY CANADA CORPORATION	29126	WISE UP HERBICIDE SOLUTION	GPI-360;	SN-SOLUTION	C
MONSANTO CANADA INC.	20423	MOCAN 943 WATER SOLUBLE HERBICIDE	GPI-120; DIC-86;	SN-SOLUTION	C
	21572	RUSTLER FALLOW LIQUID HERBICIDE	GPI-132; DIC-60;	SN-SOLUTION	C
	27200	RUSTLER LIQUID HERBICIDE	GPI-194; DIC-46;	SN-SOLUTION	C

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
	32274	ROUNDUP XTEND WITH VAPORGRIP TECHNOLOGY HERBICIDE	GPI-240; DIC-120;	SN-SOLUTION	C
	19536	RUSTLER SUMMERFALLOW HERBICIDE	GPI-108; DXB-182;	SN-SOLUTION	C
	25898	MON 77790 HERBICIDE	GPI-132; DXB-82;	SN-SOLUTION	C
	25604	ROUNDUP FAST FORWARD PREHARVEST HERBICIDE	GPI-300; GLG-16;	SN-SOLUTION	C
	25795	ROUNDUP FASTFORWARD PRESEED	GPI-300; GLG-10;	SN-SOLUTION	C
	25918	MON 77759 WATER SOLUBLE HERBICIDE	GPI-300; GLG-36;	SN-SOLUTION	C
	26625	MON 78027 WATER SOLUBLE HERBICIDE	GPI-180; GLG-131;	SN-SOLUTION	C
	26920	ROUNDUP TRANSORB MAX LIQUID HERBICIDE	GPI-480;	SN-SOLUTION	C
	29841	MON 76431 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C
	29868	MON 76429 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C
	19899	VISION SILVICULTURE HERBICIDE	GPI-356;	SN-SOLUTION	C+R
	25344	ROUNDUP TRANSORB LIQUID HERBICIDE	GPI-360;	SN-SOLUTION	C+R
	27487	ROUNDUP WEATHERMAX WITH TRANSORB 2 TECHNOLOGY LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	27736	VISIONMAX SILVICULTURE HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	27764	ROUNDUP ULTRA LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	27946	RENEGADE HC LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	28198	ROUNDUP TRANSORB HC LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	28486	ROUNDUP ULTRA 2 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	28487	RT/540 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	28608	MON 79828 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	28609	MON 79791 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	29498	START UP HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	30104	MON 76669	GPP-540;	SN-SOLUTION	C+R
	32209	POWERMAX HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	32356	ROUNDUP CUSTOM FOR AQUATIC AND TERRESTRIAL USE	GPI-;	SN-SOLUTION	R

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
		LIQUID HERBICIDE			
NEWAGCO INC	29290	MPOWER GLYPHOSATE	GPI-356;	SN-SOLUTION	C
NUFARM AGRICULTURE INC.	30870	GLYKAMBA HERBICIDE	GPI-194; DIC-46;	SN-SOLUTION	C
	25866	NUFARM CREDIT LIQUID HERBICIDE	GPI-356;	SN-SOLUTION	C
	27950	CREDIT PLUS LIQUID HERBICIDE	GPI-360;	SN-SOLUTION	C
	29124	CREDIT 45 HERBICIDE	GPI-450;	SN-SOLUTION	C
	29125	NUFARM CREDIT 360 LIQUID HERBICIDE	GPI-360;	SN-SOLUTION	C
	29470	NUGLO HERBICIDE	GPI-450;	SN-SOLUTION	C
	29479	POLARIS	GPI-360;	SN-SOLUTION	C
	29480	NUFARM GLYPHOSATE 360 HERBICIDE	GPI-360;	SN-SOLUTION	C
	29888	CREDIT XTREME HERBICIDE	GPO-540;	SN-SOLUTION	C
	31316	CARNIVAL 540 HERBICIDE	GPO-540;	SN-SOLUTION	C
PRODUCTIERRA	31063	SMOKE 41% GLYPHOSATE	GPI-360;	SN-SOLUTION	C
RACK PETROLEUM LTD.	30442	THE RACK GLYPHOSATE	GPI-360;	SN-SOLUTION	C
	31314	RACKETEER	GPI-360;	SN-SOLUTION	C
SHARDA CROPCHEM LIMITED	31493	SHARDA GLYPHOSATE 360	GPI-360;	SN-SOLUTION	C
	32122	GLYFO SILVI HERBICIDE	GPI-360;	SN-SOLUTION	C+R
SYNGENTA CANADA INC.	29341	HALEX GT HERBICIDE	MER-25; GPP-250; AME-250;	SN-SOLUTION	C
	29552	TAKKLE HERBICIDE	GPI-140; DIC-70;	SN-SOLUTION	C
	30412	FLEXSTAR GT HERBICIDE	GPM-271; FOF-67;	SN-SOLUTION	C
	28802	CYCLE HERBICIDE	GPP-500;	SN-SOLUTION	C
	31711	CALLISTO GT HERBICIDE	MER-45.5; GPP-455;	SU-SUSPENSION	C
	27192	TOUCHDOWN IQ LIQUID HERBICIDE	GPM-360;	SN-SOLUTION	C+R
	28072	TOUCHDOWN TOTAL HERBICIDE	GPP-500;	SN-SOLUTION	C+R
	29201	TRAXION HERBICIDE	GPP-500;	SN-SOLUTION	C+R
TERAGRO INC	29022	WEED-MASTER GLYPHOSATE 41 HERBICIDE	GPS-356;	SN-SOLUTION	C
	29009	WEED-MASTER GLYPHOSATE FORESTRY HERBICIDE	GPI-356;	SN-SOLUTION	C+R
UNITED PHOSPHORUS INC.	30366	GLYPHO 41 HERBICIDE	GPI-356;	SN-SOLUTION	C+R
UNIVAR CANADA LTD.	32228	GUARDSMAN GLYPHOSATE	GPO-540;	SN-SOLUTION	C
DOW AGROSCIENCES CANADA INC.	27351	GLYPHOSATE 18% HERBICIDE SOLUTION CONCENTRATE	GPI-143;	SN-SOLUTION	D

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
	27352	GLYPHOSATE 0.96% HERBICIDE READY-TO-USE	GPI-7;	SN-SOLUTION	D
FMC CORPORATION	26609	GLYFOS HERBICIDE 143 CONCENTRATE	GPI-143;	SN-SOLUTION	D
	26610	GLYFOS HERBICIDE 7 READY-TO-USE	GPI-7;	SN-SOLUTION	D
	26827	GLYFOS CONCENTRATE 356 HERBICIDE	GPI-356;	SN-SOLUTION	D
MONSANTO CANADA INC.	22627	ROUNDUP CONCENTRATE NON-SELECTIVE HERBICIDE	GPI-143;	SN-SOLUTION	D
	22759	ROUNDUP SUPER CONCENTRATE GRASS & WEED CONTROL	GPI-356;	SN-SOLUTION	D
	22807	ROUNDUP READY TO USE NON-SELECTIVE HERBICIDE WITH FASTACT FOAM	GPI-7;	SN-SOLUTION	D
	24299	ROUNDUP READY-TO-USE GRASS & WEED CONTROL WITH FASTACT FOAM	GPI-7;	SN-SOLUTION	D
	26263	ROUNDUP READY-TO-USE WITH FASTACT FOAM PULL'N SPRAY NON-SELECTIVE HERBICIDE	GPI-7;	SN-SOLUTION	D
	27460	ROUNDUP READY-TO-USE NON-SELECTIVE HERBICIDE	GPI-7.2;	SN-SOLUTION	D
	27506	ROUNDUP READY-TO-USE PULL'N SPRAY NON-SELECTIVE HERBICIDE	GPI-14.0;	SN-SOLUTION	D
	27507	ROUNDUP READY-TO-USE PULL'N SPRAY TOUGH BRUSH & POISON IVY CONTROL NON-SELECTIVE HERBICIDE	GPI-14.0;	SN-SOLUTION	D
	28974	ROUNDUP PUMP 'N GO	GPI-7;	SN-SOLUTION	D
	29003	ROUNDUP READY-TO-USE POISON IVY & BRUSH CONTROL NON-SELECTIVE HERBICIDE	GPI-14;	SN-SOLUTION	D
	29034	ROUNDUP READY-TO-USE POISON IVY & BRUSH CONTROL WITH QUICK CONNECT SPRAYER	GPI-14;	SN-SOLUTION	D
	31153	REFILL FOR ROUNDUP READY-TO-USE WITH WAND APPLICATOR	GPI-7.0;	SN-SOLUTION	D
	31154	ROUNDUP READY-TO-USE WITH WAND APPLICATOR	GPI-7.0;	SN-SOLUTION	D
	31514	ROUNDUP READY-TO-USE REFILL	GPI-7;	SN-SOLUTION	D

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
	31997	ROUNDUP READY-TO-USE TOUGH BRUSH & POISON IVY CONTROL WITH WAND APPLICATOR	GPI-14.0;	SN-SOLUTION	D
	32041	REFILL FOR ROUNDUP READY-TO-USE TOUGH BRUSH & POISON IVY CONTROL WITH WAND APPLICATOR	GPI-14;	SN-SOLUTION	D
	23786	ROUNDUP QUIK STIK NON-SELECTIVE HERBICIDE TABLETS	GPS-60;	TA-TABLET	D
LES PRODUITS DE CONTROLE SUPERIEUR INC/SUPERIOR CONTROL PRODUCTS INC	28464	TOTALEX CONCENTRATE BRUSH, GRASS & WEED KILLER HOME GARDENER	GPI-143;	SN-SOLUTION	D
	28467	BYEBYE WEED CONCENTRATE BRUSH, GRASS & WEED KILLER	GPI-143;	SN-SOLUTION	D
	28469	BYEBYE WEED READY-TO-USE BRUSH, GRASS & WEED KILLER	GPI-7;	SN-SOLUTION	D
	28470	TOTALEX READY-TO-USE BRUSH, GRASS & WEED KILLER HOME GARDENER	GPI-7;	SN-SOLUTION	D
	28471	TOTALEX SUPER CONCENTRATE BRUSH, GRASS & WEED KILLER HOME GARDENER	GPI-356;	SN-SOLUTION	D
	28472	BYEBYE WEED SUPER CONCENTRATE BRUSH, GRASS & WEED KILLER	GPI-356;	SN-SOLUTION	D
	28574	TOTALEX RTU BRUSH, GRASS & WEED KILLER WITH 1 TOUCH POWER SPRAYER HOME	GPI-7.0;	SN-SOLUTION	D
	28575	BYEBYE WEED RTU BRUSH, GRASS & WEED KILLER WITH 1 TOUCH POWER SPRAYER	GPI-7.0;	SN-SOLUTION	D
	28576	TOTALEX EXTRA STRENGTH RTU BRUSH, GRASS & WEED KILLER WITH 1 TOUCH POWER SPRAYER HOME GARDENER	GPI-14;	SN-SOLUTION	D
	28577	TOTALEX EXTRA STRENGTH RTU BRUSH, GRASS & WEED KILLER WITH 1 TOUCH POWER	GPI-14;	SN-SOLUTION	D

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
		SPRAYER VIRTERRA			
SURE-GRO IP INC.	27013	WILSON TOTAL WIPEOUT MAX GRASS & WEED KILLER READY TO USE	GPI-7;	SN-SOLUTION	D
	27014	WILSON TOTAL WIPEOUT MAX GRASS & WEED KILLER CONCENTRATE	GPI-143;	SN-SOLUTION	D
	27015	LATER'S GRASS & WEED KILLER SUPER CONCENTRATE	GPI-356;	SN-SOLUTION	D
	29580	WILSON TOTAL WIPEOUT MAX GRASS & WEED KILLER READY TO USE BATTERY POWERED	GPI-7;	SN-SOLUTION	D
	31023	SMARTONES WIPEOUT MAX	GPI-7.0;	SN-SOLUTION	D
	32090	WILSON TOTAL WIPEOUT MAX GRASS & WEED KILLER REFILL	GPI-7;	SN-SOLUTION	D
DOW AGROSCIENCES CANADA INC.	26449	GLYPHOSATE 62% SOLUTION MANUFACTURING CONCENTRATE	GPI-46;	SN-SOLUTION	M
	27074	VANTAGE HERBICIDE SOLUTION MANUFACTURING CONCENTRATE	GPI-356;	SN-SOLUTION	M
	27075	VANTAGE PLUS HERBICIDE SOLUTION MANUFACTURING CONCENTRATE	GPI-360;	SN-SOLUTION	M
	28963	GLYPHOSATE 85% MANUFACTURING CONCENTRATE	GPS-85;	SN-SOLUTION	M
	28783	GF-1667 HERBICIDE MANUFACTURING CONCENTRATE	GPX-49;	SN-SOLUTION	M
FMC CORPORATION	25600	GLYPHOSATE CONCENTRATE HERBICIDE	GPI-46.3;	SN-SOLUTION	M
	27497	GLYFOS 356 MUC	GPI-356;	SN-SOLUTION	M
MONSANTO CANADA INC.	21061	MON 0139 SOLUTION HERBICIDE MANUFACTURING CONCENTRATE	GPI-46.0;	SN-SOLUTION	M
	26919	MON 77945 HERBICIDE MANUFACTURING CONCENTRATE SOLUTION	GPI-46;	SN-SOLUTION	M
	28625	MON 78087 HERBICIDE MANUFACTURING CONCENTRATE	GPI-356;	SN-SOLUTION	M
	32273	GLY 135EA HERBICIDE MANUFACTURING CONCENTRATE	GPI-45.6;	SN-SOLUTION	M

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
	27485	MON 78623 HERBICIDE MANUFACTURING CONCENTRATE	GPP-47.3;	SN-SOLUTION	M
	28603	MON 79380 HERBICIDE MANUFACTURING CONCENTRATE	GPP-540;	SN-SOLUTION	M
	28604	MON 79582 HERBICIDE MANUFACTURING CONCENTRATE	GPP-540;	SN-SOLUTION	M
	28605	MON 79544 HERBICIDE MANUFACTURING CONCENTRATE	GPP-540;	SN-SOLUTION	M
	27183	MON 77973 HERBICIDE MANUFACTURING CONCENTRATE	GPS-85;	SN-SOLUTION	M
NUA	29123	NUFARM GLYPHOSATE IPA MANUFACTURING CONCENTRATE	GPI-46;	SN-SOLUTION	M
SYNGENTA CANADA INC.	27871	GLYPHOSATE 600 SL MANUFACTURING CONCENTRATE	GPS-600;	SN-SOLUTION	M
WMW	29719	TERAGRO GLYPHOSATE MANUFACTURING CONCENTRATE	GPI-46;	SN-SOLUTION	M
ALBAUGH LLC	28321	CLEAROUT GLYPHOSATE TECHNICAL	GPS-94.8;	SO-SOLID	T
AGROMARKETING CO. INC.	29645	NASA GLYPHOSATE TECHNICAL	GPS-96.37;	SO-SOLID	T
CONSUS CHEMICALS, LLC.	31728	CONSUS GLYPHOSATE TECHNICAL	GPS-96.7;	SO-SOLID	T
DOW AGROSCIENCES CANADA INC.	26450	GLYPHOSATE TECHNICAL HERBICIDE	GPS-96.3;	SO-SOLID	T
	28967	TECHNICAL GLYPHOSATE HERBICIDE	GPS-96.2;	SO-SOLID	T
FMC CORPORATION	24337	GLYPHOSATE TECHNICAL	GPS-85.8;	SO-SOLID	T
	29143	GLYFOS SOLUBLE CONCENTRATE HERBICIDE 2	GPS-97.9;	SO-SOLID	T
	29326	CHEMINOVA GLYPHOSATE TECHNICAL II	GPS-95.7;	SO-SOLID	T
	29530	CHEMINOVA GLYPHOSATE TECHNICAL III	GPS-98.2;	SO-SOLID	T
JOINT GLYPHOSATE TASK FORCE, LLC	30638	JOINT GLYPHOSATE TECHNICAL	GPS-96.3;	SO-SOLID	T
LIBERTAS NOW INC.	29265	KNOCKOUT TECH	GPS-98.1;	SO-SOLID	T
MEY CORPORATION	29799	MEY CORP GLYPHOSATE TECHNICAL	GPS-98.5;	SO-SOLID	T
	30099	MGT GLYPHOSATE TECHNICAL	GPS-96.4;	SO-SOLID	T
	30617	MEY GLYPHOSATE SHANRG TECHNICAL	GPS-97.59;	SO-SOLID	T

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
MONSANTO CANADA INC.	19535	GLYPHOSATE TECHNICAL GRADE	GPS-96.3;	SO-SOLID	T
NEWAGCO INC	29381	NEWAGCO GLYPHOSATE TECHNICAL	GPS-96.0;	SO-SOLID	T
NUFARM AGRICULTURE INC.	28857	NUFARM GLYPHOSATE TECHNICAL ACID	GPS-96.5;	SO-SOLID	T
PRODUCTIERRA	31062	PRODUCTIERRA GLYPHOSATE TECHNICAL	GPS-98.0;	SO-SOLID	T
SHARDA CROPCHEM LIMITED	29980	SHARDA GLYPHOSATE TECHNICAL HERBICIDE	GPS-96.2;	SO-SOLID	T
SYNGENTA CANADA INC.	28983	TECHNICAL TOUCHDOWN HERBICIDE	GPS-97.1;	SO-SOLID	T
	29540	TOUCHDOWN TECHNICAL HERBICIDE	GPS-99;	SO-SOLID	T
UPI GLYPHOSATE TECHNICAL HERBICIDE	30634	UPI GLYPHOSATE TECHNICAL HERBICIDE	GPS-97.7;	SO-SOLID	T
TERAGRO INC	28882	GLYPHOSATE TECHNICAL HERBICIDE	GPS-97.5;	SO-SOLID	T

[1] GPS = glyphosate acid, GPI = glyphosate isopropylamine or ethnolamine salt, GPM = glyphosate mono-ammonium or diammonium salt, GPP = glyphosate potassium salt, GPX = glyphosate dimethylsulfonium salt, and GPO = GPI + GPP. Note that GPT (glyphosate trimethylsulfonium salt) has been voluntarily discontinued by the registrant Syngenta Canada Inc.

[2] C = Commercial Class, C+R = Commercial and Restricted Class, D = Domestic Class, M = Manufacturing Concentrate, T = Technical grade active ingredient.

[3] AME = s-metolachlor, DIC = dicamba, DIQ = diquat, DXB = 2,4-D (isomer specific), FOF = fomesafen, GLG = glufosinate ammonium and MER = mesotrione.

Appendix III Summary of Species sensitivity Distribution Toxicity Data

Table 1 Revised summary of Species Sensitivity Distribution (SSDs) toxicity data analysis for glyphosate herbicide: HC_5 [1] or the most sensitive endpoints are listed by taxonomic group for Fish, Aquatic Invertebrates and Amphibians *

Test material	Exposure	Freshwater invertebrates (mg a.e./L)[B]	Freshwater fish (mg a.e./L)[C]	Marine fish (mg a.e./L)[C]	Marine invertebrates (mg a.e./L)[B]	Amphibians (mg a.e./L)[C]	Amphibians Mesocosm/field (mg a.e./L)[C]
TGAI	Acute	HC_5: 15.9	HC_5: 70	HC_5: 19.9	HC_5: 4.7	HC_5: 14.9	-
	Chronic	NOEC: 13.0	NOEC: 22.4	NOEC: 0.1	-	-	-
EUP NON POEA	Acute	HC_5: 24.4	HC_5: 2.3	LC_{50}: 114.6	EC_{50}: 23.2	HC_5: 13.9	-
	Chronic	EC_{50}: 44.0	-	-	-	-	-
EUP WITH POEA	Acute	HC_5: 0.1	HC_5: 2.2	HC_5: 3.0	HC_5: 0.1	HC_5: 0.73	HC_5: 3.7 HC_5: 3.3 (kg a.e/ha)
	Chronic	NOEC: 0.2	NOEC: 0.28	-	-	HC_5: 0.43	HC_5: 1.9
AMPA	Acute	LC_{50}: 316.0	LC_{50}: 274.0	-	EC_{50}: 97.0	-	-
	Chronic	-	-	-	-		-
POEA	Acute	HC_5: 0.004	HC_5: 0.2	HC_5: 2.0	EC_{50}: 0.6	HC_5: 0.3	-
	Chronic	-	-	-	-	-	-

*Where SSDs could not be determined, the most sensitive species endpoint value is reported; [1]Hazardous concentration to 5% of species; POEA is a formulant, POEA concentrations cannot be directly compared to other data as the concentration in a formulation varies and not specified; [B] HC_5 is derived from EC_{50} values; [C] HC_5 is derived from LC_{50} values.
TGAI = Technical grade active ingredient, EUP NON POEA = End-use product that does not contain polyethoxylated tallow amine compound in their formulation, EUP WITH POEA = End-use product that does contain polyethoxylated tallow amine compound in their formulation, AMPA = aminmethylphosphonic acid compound, POEA = polyethoxylated tallow amine

Table 2 Revised summary of Species Sensitivity Distribution (SSDs) toxicity data analysis for glyphosate herbicide: HC_5 [1] or the most sensitive endpoints are listed by taxonomic group for Aquatic Plants, Algae, Terrestrial Plants *

Test material	Exposure	Freshwater Algae (mg a.e./L)[B]	Freshwater Plants (mg a.e./L)	Marine Algae (mg a.e./L)	Snails (mg a.e./L)
TGAI	Acute	HC_5: 6.6 EC_{50}: 10.1	EC_{50}: 17.3 Er_{50}: 0.38 kg a.e./ha	EC_{50}: 3.35	-
	Chronic	HC_5:21.6	-	EC_{50}:101.5	NOEC: 1000
EUP NON POEA	Acute	EC_{50}: 37	-	-	-
	Chronic	-	-	-	NOEC: 29.7 NOEC: 219 (mg a.e./kg soil)
EUP WITH POEA	Acute	HC_5: 0.1	EC_{50}: 2.1	EC_{50}: 0.43	LC_{50}: 2.3
	Chronic	HC_5:0.3		EC_{50}: 8.3	NOEC: 8.55
EUP NON POEA and WITH POEA	Acute	-	-	-	-

Test material	Exposure	Freshwater Algae (mg a.e./L)[B]	Freshwater Plants (mg a.e./L)	Marine Algae (mg a.e./L)	Snails (mg a.e./L)
AMPA	Acute	EC_{50}: 73	-	-	-
	Chronic	-	-	-	-
POEA	Acute	EC_{50}: 4	-	EC_{50}: 3.4	-

*Where SSDs could not be determined, the most sensitive species endpoint value is reported; [I]Hazardous concentration to 5% of species; POEA is a formulant, POEA concentrations cannot be directly compared to other data as the concentration in a formulation varies and not specified; [B] HC_5 is derived from EC_{50} values; [C] HC_5 is derived from LC_{50} values;
TGAI = Technical grade active ingredient, EUP NON POEA = End-use product that does not contain polyethoxylated tallow amine compound in their formulation, EUP WITH POEA = End-use product that does contain polyethoxylated tallow amine compound in their formulation, AMPA = aminmethylphosphonic acid compound, POEA = polyethoxylated tallow amine

Table 3 Revised summary of Species Sensitivity Distribution (SSDs) toxicity data analysis for glyphosate herbicide: HC_5 [I] or the most sensitive endpoints are listed by taxonomic group for Terrestrial Plants and Terrestrial Invertebrates.

Test material	Exposure	Terrestrial Plants (SE) EC_{50} (kg a.e/ha)	Terrestrial plants EC_{25} Mixed[D] (kg a.e/ha)	Terrestrial plants E_{C50} Mixed[D] (kg a.e/ha)	Earthworms (mg a.e./kg soil)
TGAI	Acute	EC_{50}: 0.07	-		690
	Chronic	-	-		-
EUP NON POEA	Acute	EC_{50}: 4.48	-		-
	Chronic	-	-		-
EUP WITH POEA	Acute	-	HD_5 = 0.035		0.253
	Chronic	-	-		-
EUP NON POEA and WITH POEA	Acute	-	HD_5 = 0.037	HD_5 = 0.0658	-

(SE) = seedling emergence, (VV) = vegetative vigor; *Where SSDs could not be determined, the most sensitive species endpoint value is reported; [I]Hazardous concentration to 5% of species; POEA is a formulant, POEA concentrations cannot be directly compared to other data as the concentration in a formulation varies and not specified; [B] HC_5 is derived from EC_{50} values; [C] HC_5 is derived from LC_{50} values; [D]Mixed = Crop and non-crop plants combined. Yellow highlight: most sensitive acute and chronic endpoint.
TGAI = Technical grade active ingredient, EUP NON POEA = End-use product that does not contain polyethoxylated tallow amine compound in their formulation, EUP WITH POEA = End-use product that does contain polyethoxylated tallow amine compound in their formulation, AMPA = aminmethylphosphonic acid compound, POEA = polyethoxylated tallow amine

Appendix IV Label Amendments for Products Containing Glyphosate

The label amendments presented below do not include all label requirements for individual products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the following label statements.

A) Label Amendments for Glyphosate Technical Products

The following label amendments are required on the Glyphosate Technical labels:

1) Add to the primary panel of the Technical product labels:

   The signal words "DANGER – EYE IRRITANT", and accompanying glyphs.

2) Before **STORAGE section, Add** the title "**ENVIRONMENTAL HAZARDS**" and the following statement:

   - **TOXIC** to non-target terrestrial plants
   - **TOXIC** to aquatic organisms

3) **Remove** the following statement under the "**DISPOSAL AND DECONTAMINATION**"

   "Canadian formulators of this technical should dispose of unwanted active and containers in accordance with municipal or provincial regulations. For information on disposal of unused, unwanted product, contact the manufacturer or the provincial regulatory agency. Contact the manufacturer and the provincial regulatory agency in the case of a spill, and for clean-up of spills."

   and replace it with the following statement:

   "Canadian manufacturers should dispose of unwanted active ingredients and containers in accordance with municipal or provincial regulations. For additional details and clean up of spills, contact the manufacturer or the provincial regulatory agency."

B) For Domestic Products Containing Glyphosate

For all end-use products, the following statement is required:

"Glyphosate is not to be applied using hand-wicking or hand-daubing methods."

C) For Commercial and Agricultural Class Products Containing Glyphosate

1) Add to DIRECTIONS FOR USE:

For all end-use products, the following statement is required:

"Glyphosate is not to be applied using hand-wicking or hand-daubing methods."

Restricted Entry Intervals

"The restricted entry interval is 12 hours after application for all agricultural uses."

2) **Add to Use Precautions**

"Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings."

3) **Add the following to ENVIRONMENTAL HAZARDS:**

- **TOXIC** to aquatic organisms and non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.
- To reduce runoff from treated areas into aquatic habitats, avoid application to areas with a moderate to steep slope, compacted soil or clay.
- Avoid application when heavy rain is forecast.
- Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

4) **Add to DIRECTIONS FOR USE**

The following statement is required for all agricultural and commercial pesticide products:

- **As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests**
- **DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.**

5) Add to **DIRECTIONS FOR USE**

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) coarse classification. Boom height must be 60 cm or less above the crop or ground.

Airblast or mist blower application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side. For airblast applications, turn off outward pointing nozzles at row ends and outer rows.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) coarse classification. To reduce drift caused by turbulent wingtip vortices, the nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing- or rotorspan.

Buffer zones:

Use of the following spray methods or equipment **DO NOT** require a buffer zone: hand-held or backpack sprayer and spot treatment, inter-row hooded sprayer, low-clearance hooded or shielded sprayers that ensure spray drift does not come in contact with orchard crop fruit or foliage, soil drench and soil incorporation.

For application to rights-of-way and for forestry uses, buffer zones for protection of sensitive terrestrial habitats are not required; however, the best available application strategies which minimize off-site drift, including meteorological conditions (for example, wind direction, low wind speed) and spray equipment (for example, coarse droplet sizes, minimizing height above canopy), should be used. Applicators must, however, observe the specified buffer zones for protection of sensitive aquatic habitats.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands) and sensitive aquatic habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs, wetlands and estuarine/marine water bodies).

Table 1 Buffer Zones for the Protection of Aquatic and Terrestrial Habitats from Spray Drift of Glyphosate Products Formulated with POEA

Agricultural, forestry and non-cropland systems		Maximum number of applications	Buffer Zones (metres) Required for the Protection of:	
			Aquatic habitats	Terrestrial habitats
Agricultural crop system and ground boom application method				
Rye, cranberry, pasture, summer fallow, all other crops for pre-seeding treatments only, filberts or hazelnut at pre-seeding only, ginseng new garden		1	1	1
Ginseng - existing established garden, Canola – Roundup Ready hybrid for seed production		2	1	1
Filberts or hazelnut, sugar beets (glyphosate tolerant varieties)		4	1	1
Corn (glyphosate non-tolerant varieties including grain, silage and ornamental types), sugar beet (glyphosate non-tolerant varieties), strawberry, blueberry highbush and lowbush, walnut, chestnut, Japanese heartnut, Turf grass (prior to establishment or renovation)		2	1	2
Wheat, barley, oats, soybean (glyphosate non-tolerant varieties), corn-sweet (glyphosate tolerant varieties), canola (glyphosate non-tolerant varieties), peas, dry beans, flax (including low linolcic acid varieties), lentils, chickpea, lupin (dried), fava bean (dried), mustard (yellow/white, brown, oriental), pearl millet, sorghum (grain) (not for use as a forage crop), asparagus, corn (glyphosate tolerant varieties), forage grasses and legume including seed production		3	1	2
Canola (glyphosate tolerant varieties), soybean (glyphosate tolerant varieties)		4	1	2
Apple, apricot, cherry (sweet/sour), peaches, pears, plums, grapes		3	1	3
Agricultural crop system and airblast application method (including mist blower)				
Pasture		1	20	30
Turfgrass (Prior to establishment or renovation)		2	25	35
Forest plant system and ground boom application method				
Forest and woodlands > 500 ha Site preparation		2	1	NR
Forest plant system and airblast application method (including mist blower)				
Forest and woodlands > 500 ha Site preparation		2	1	NR
Non-cropland system and ground boom application method				
Non-crop land and industrial uses: Industrial and rights of way areas, Recreational and public areas		3	1	3*
Non-cropland system and airblast application method (including mist blower)				
Non-crop land and industrial uses: Industrial and rights of way areas, Recreational and public areas		3	1	30*
Agricultural crop system and aerial application method	**Wing type**			
Rye, corn (glyphosate non-tolerant varieties), corn-sweet (glyphosate tolerant varieties), chickpea, lupin (dried), fava bean (dried), mustard (yellow/white, brown, oriental), pearl millet , sorghum (grain) (not for use as a forage crop), sugar beet (glyphosate non-tolerant varieties), all other crops for pre-seeding treatments only	Fixed and rotary wing	1	15	20

Agricultural, forestry and non-cropland systems		Maximum number of applications	Buffer Zones (metres) Required for the Protection of:	
			Aquatic habitats	Terrestrial habitats
Canola (glyphosate tolerant varieties)	Fixed and rotary wing	3	20	40
Sugar beets (glyphosate tolerant varieties)	Fixed wing	2	20	30
	Rotary wing	2	15	30
Wheat, barley, oats, soybean (glyphosate non-tolerant varieties), canola (glyphosate non-tolerant varieties), peas, dry beans, flax (including low linolcic acid varieties), lentils	Fixed wing	2	20	35
	Rotary wing	2	20	30
Forage grasses and legume including seed production	Fixed and rotary wing	1	20	40
Soybean (glyphosate tolerant varieties)	Fixed wing	3	20	45
	Rotary wing	3	20	40
Summer fallow	Fixed wing	1	20	45
	Rotary wing	1	20	40
Corn (glyphosate tolerant varieties)	Fixed wing	2	20	50
	Rotary wing	2	20	45
Pasture	Fixed wing	1	30	70
	Rotary wing	1	30	55
Forestry system and aerial application method				
Forest and woodlands >500 ha Site preparation	Fixed wing	2	10	NR
	Rotary wing	2	1	NR
Forest and woodlands <500 ha Site preparation	Fixed wing	2	5	NR
	Rotary wing	2	1	NR
Non-cropland system and aerial application method				
Non-crop land and industrial uses: rights-of way areas only	Fixed wing	3	100	NR
	Rotary wing	3	60	NR

* Buffer zones for the protection of terrestrial habitats are not required for forestry uses or for use on rights-of-way including railroad ballast, rail and hydro rights-of-way, utility easements, roads, and training grounds and firing ranges on military bases.
NR = Buffer zones for the protection of terrestrial habitats are not required for forestry uses.

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

Table 2 Buffer Zones for the Protection of Aquatic and Terrestrial Habitats from Spray Drift of Glyphosate Products without POEA

Agricultural and non-cropland systems		Maximum number of applications	Buffer Zones (metres) Required for the Protection of:	
			Aquatic habitats	Terrestrial habitats
Agricultural crop system and ground boom application method				
Rye, cranberry, pasture, summer fallow, pasture, all other crops for pre-seeding treatments only, filberts or hazelnut pre-seeding only, ginseng new garden		1	1	1
Ginseng - existing established garden, Canola – Roundup Ready hybrid for seed production		2	1	1
Filberts or hazelnut, sugar beets (glyphosate tolerant varieties)		4	1	1
Corn (glyphosate non-tolerant varieties including grain, silage and ornamental types), sugar beet (glyphosate non-tolerant varieties), strawberry, blueberry highbush and lowbush, walnut, chestnut, Japanese heartnut, Turf grass (prior to establishment or renovation)		2	1	2
Wheat, barley, oats, soybean (glyphosate non-tolerant varieties), corn-sweet (glyphosate tolerant varieties), canola (glyphosate non-tolerant varieties), peas, dry beans, flax (including low linoleic acid varieties), lentils, chickpea, lupin (dried), fava bean (dried), mustard (yellow/white, brown, oriental), pearl millet, sorghum (grain) (not for use as a forage crop), asparagus, corn (glyphosate tolerant varieties), forage grasses and legume including seed production		3	1	2
Canola (glyphosate tolerant varieties), soybean (glyphosate tolerant varieties)		4	1	2
Apple, apricot, cherry (sweet/sour), peaches, pears, plums, grapes		3	1	3
Agricultural crop system and airblast application method (including mist blower)				
Pasture		1	20	30
Turfgrass (Prior to establishment or renovation)		2	25	35
Non-cropland system and ground boom application method				
Non-crop land and industrial uses: Industrial and rights of way areas, Recreational and public areas		3	1	3
Non-cropland system and airblast application method (including mist blower)				
Non-crop land and industrial uses: Industrial and rights of way areas, Recreational and public areas		3	20	30
Agricultural crop system and aerial application method				
Rye, corn (glyphosate non-tolerant varieties), corn-sweet (glyphosate tolerant varieties), chickpea, lupin (dried), fava bean (dried), mustard (yellow/white, brown, oriental), pearl millet , sorghum (grain) (not for use as a forage crop), sugar beet (glyphosate non-tolerant varieties), all other crops for pre-seeding treatments only	Fixed and rotary wing	1	15	20

Agricultural and non-cropland systems		Maximum number of applications	Buffer Zones (metres) Required for the Protection of:	
			Aquatic habitats	Terrestrial habitats
Sugar beets (glyphosate tolerant varieties)	Fixed wing	2	20	30
	Rotary wing	2	15	30
Wheat, barley, oats, soybean (glyphosate non-tolerant varieties), canola (glyphosate non-tolerant varieties), peas, dry beans, flax (including low linoleic acid varieties), lentils	Fixed wing	2	20	35
	Rotary wing	2	20	30
Forage grasses and legume including seed production	Fixed and rotary wing	1	20	40
Canola (glyphosate tolerant varieties)	Fixed and rotary wing	3	20	40
Soybean (glyphosate tolerant varieties)	Fixed wing	3	20	45
	Rotary wing	3	20	40
Summer fallow	Fixed wing	1	20	45
	Rotary wing	1	20	40
Corn (glyphosate tolerant varieties)	Fixed wing	2	20	50
	Rotary wing	2	20	45
Pasture	Fixed wing	1	30	70
	Rotary wing	1	30	55
Non-cropland system and aerial application method				
Non-crop land and industrial uses: rights-of way areas only	Fixed wing	3	100	NR
	Rotary wing	3	60	NR

* Buffer zones for the protection of terrestrial habitats are not required for use on rights-of-way including railroad ballast, rail and hydro rights-of-way, utility easements, roads, and training grounds and firing ranges on military bases.
NR = Buffer zones for the protection of terrestrial habitats are not required for forestry uses.

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

References

Studies and Information Considered in Relation to Human Health Risk Assessment

Toxicology

A. List of Additional Studies/Information submitted by Registrant – Unpublished

PMRA Document Number	Reference
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1644045	2007, Surfactant 8184-92, acute dermal toxicity study in rats, DACO: 4.6.2
1817835	2007, Surfactant, 8184-92, acute inhalation toxicity study in rats, DACO: 4.6.3
1817836	2007, Surfactant, 8184-92, skin sensitization study in guinea pigs, DACO: 4.6.6
1817838	2007, Surfactant, 8184-92, acute eye irritation study in rabbits, DACO: 4.6.4
1817839	2008, Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in rats for experimental surfactant 8184-92, DACO: 4.7.7
1817840	2007, Surfactant 8184-92, acute oral toxicity study (UDP) in rats, DACO: 4.6.5
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Dietary Exposure

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